VOLUME 15 NUMBER 5

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ARCHIVES OF SURGERY

VOLUME 15 NOVEMBER, 1927 NUMBER 5

SUBUNGUAL MELANOMA

HUTCHINSON'S MELANOTIC WHITLOW *

NATHAN A. WOMACK, M.D.

ST. LOUIS

Subungual melanoma is given a somewhat inconspicuous place in the usual discussion of melanotic tumors. It appears to be a much more common lesion than the small number of reported cases would suggest. In four of the twenty-six patients with melanoma who were treated at the Barnes Hospital, the condition had its origin in the nail-bed. While Hutchinson [1] was the first to emphasize the lesion and give a lucid description of its clinical characteristics, attention had previously been given to it by other observers.[2] Hertzler [3] has recently published a careful review of the previously reported cases, to which he adds two. Since then, Jones [4] has described three, and Chauvenet and Dubreuilh,[5] one. I wish to add four, bringing the total of reported cases up to twenty-five.

REPORT OF CASES

CASE 1.—A white laborer, aged 53, was first admitted to Barnes Hospital on Nov. 5, 1915. A diagnosis of acute cardiac decompensation with auricular fibrillation and chronic valvular disease was made. He also had chronic, diffuse nephritis. Following digitalization and rest in bed, he improved markedly and was discharged from the hospital. He was again admitted on Dec. 10, 1917, complaining of an ulcer of the finger. For about six years previously, he had noted a pigmented spot beneath the nail of the second finger of the left hand. This lesion had not changed in size until six months before the second admission, when, following trauma, it began to grow rapidly and finally ulcerated. There was no appreciable pain.

On admission, he presented a deeply pigmented ulcer involving the lateral side of the nail-bed, with destruction of the nail in this region. The ulcer was 1.5 cm. in diameter and was surrounded by a dusky red area extending over the entire distal phalanx. The glands were not palpable in the axillary or epitrochlear regions. Because of the cardiac condition, the finger was amputated under local anesthesia, without dissection of the regional lymph nodes. The patient was

* From the Department of Surgery, Washington University School of Medicine and Barnes Hospital.

1. Hutchinson: Brit. M. J. **1**:491, 1886.
2. Boyer, quoted from Hertzler: Gaz. méd. de Paris, 1854, p. 212.
3. Hertzler, A. E.: Melanoblastoma of Nail-Bed (Melanotic Whitlow), Arch. Dermat. & Syph. **6**:701 (Dec.) 1922.
4. Jones, T. B.: Ann. Surg. **80**:839, 1924.
5. Chauvenet and Dubreuilh: Bull. et mém. Soc. nat. de Chir. **5**:143, 1927.

Collected Cases of Subungual Melanoma

Author	Site	Age	Sex	Trauma	Duration	Treatment	Course
Boyer [3]	Finger	57	♂	Negative	2 years	Amputation	?
Demargnay and Monad [3]	Thumb	59	♀	Negative	Several months	?	?
Annendale [3]	Finger	56	?	Negative	15 months	Amputation	?
Nieberg [3]	Thumb	51	♂	Positive	1½ years	Amputation	Dead
Willett [3]	Thumb	80	♀	Negative	?	Amputation	Recurrence 3 years later in axilla
Sacin and Keser [3]	Finger	62	♂	Positive	6 years	Amputation	?
Halle [3]	Thumb	46	♂	Negative	7 years	Amputation	?
Hutchinson [2]	?	Middle age	♂	Negative	?	Amputation	Recurrence in axillary glands from 8 to 10 years
	Thumb	Middle age	♂	Negative	Several years	?	?
Lediard [3]	Finger	40	♀	Negative	2 years	Amputation	2 years; dead from metastases
Faguet [3]	Finger	63	♀	Positive	?	Amputation and axillary dissection	?
Coley, W. B.[3]	Thumb	37	♂	Positive	?	Amputation	Died of local and distal recurrence
Trimble [3]	Thumb	39	♀	Positive	2 months	Amputation	?
	Thumb	45	♂	Negative	6 months	Amputation	?
Murphy, J. B.[3]	Finger	56	♂	Negative	3 years	Amputation	3 years later had had axillary and epitrochlear recurrence
Hertzler [3]	Thumb	64	♀	Positive	1½ years	Amputation	No recurrence in 2 years
	Thumb	54	♀	Negative	4 years	Amputation	No recurrence in 2 months
Jones [4]	Thumb	42	♀	Negative	6 months	Amputation	Dead 3 years later following repeated operation for recurrence
	Toe	36	♂	Positive	2 years	Amputation	Dead 3 years later from metastases
	Toe	72	♀	Positive	5 years	Amputation	Alive 1 year
Chauvenet [5] and Dubreuilh	Little toe	48	♂	Negative	2 years	Amputation	Died with metastases 2 years afterward
Womack	Finger	53	♂	Positive	6 years	Amputation	No recurrence, 2 years
	Thumb	47	♂	Positive	2 years	Amputation	No recurrence, 4 years
	Thumb	64	♂	Negative	1 year	Amputation, axillary dissection	No recurrence, 6 months
	Finger	68	♀	?	?	Amputation, axillary dissection	Dead ?

In this table ♂ indicates male; ♀, female

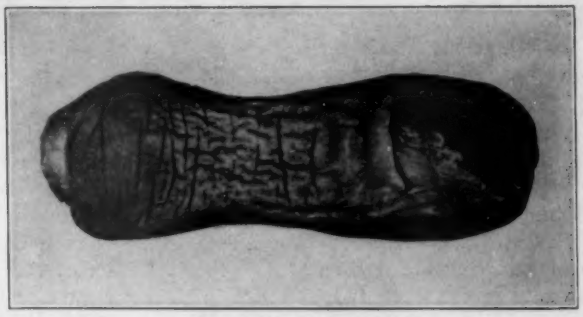

Fig. 1 (case 1).—Lateral half of the nail-bed involved by the tumor.

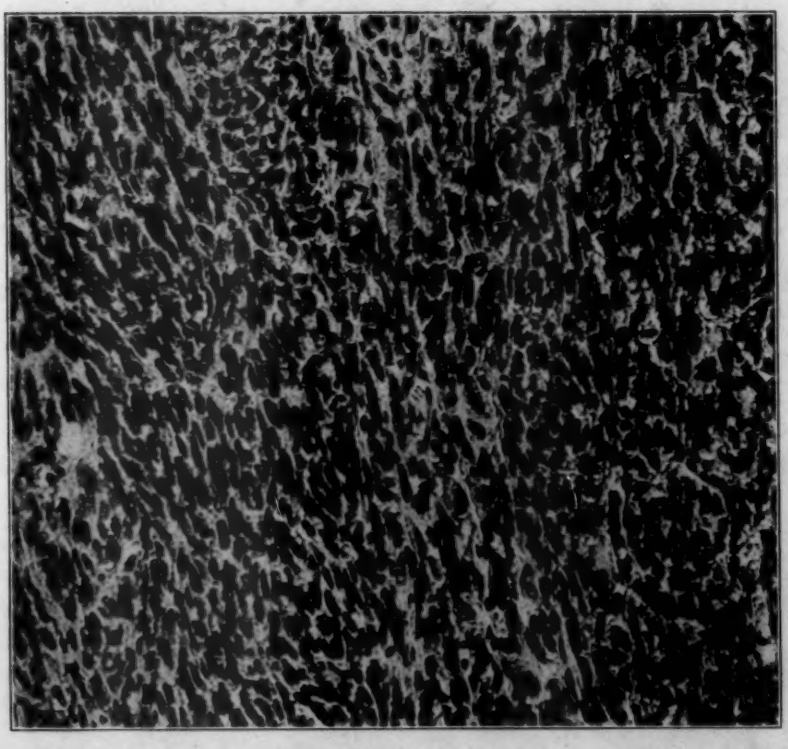

Fig. 2 (case 1).—Section taken through the base of the ulcer shown in figure 1, showing a mass of spindle cells with deeply staining nuclei and little stroma. In other areas, many round cells were present with more vesicular nuclei; mitoses were more frequent in the latter areas.

discharged eight days later. He was again treated at Barnes Hospital for heart disease in August, 1918, and later in January, 1919. There had not been any evidence of recurrence up to this time.

CASE 2.—A white laborer, aged 47, gave a history of having mashed his right thumb in 1920. It became infected, and the nail was lost. In 1921, following slight trauma, the nail was again lost, and the nail-bed ulcerated and did not heal for some time. The patient did not note any pigmentation of the ulcer. In 1922, he struck the nail slightly with a baseball, with the same sequence of events. This ulcer did not heal; it became black and caused a slight amount of pain. He was seen at Barnes Hospital in November, 1923. At this time he presented a fungating ulcer involving the dorsum of the distal phalanx of the right thumb. There was an area in the center, about 1 cm. in diameter, that was coal black; the nail was absent. The pigmented region was surrounded by a red granulating tissue that bled easily. There were palpable glands in both axillae. A roent-

Fig. 3 (case 2).—Black, fungating tumor entirely limited to the nail-bed; gray areas of necrosis are present, the result of secondary infection.

genogram of the thumb showed numerous circular, dark areas in the tuft of the distal phalanx, with questionable dissolution of the cortex at several points. The thumb was amputated at the metacarpophalangeal articulation. Axillary dissection was refused. The postoperative course was uneventful. There has not been any evidence of recurrence of the tumor up to the present time.

CASE 3.—A white man, aged 64, noted a linear pigmentation in the lateral nail-bed of the right thumb in April, 1926. The distal phalanx of the thumb began to swell and to become red. Only a slight amount of tenderness was present. The nail-bed was incised by a physician, but pus was not obtained. The incision did not heal, and in its place there appeared a coal-black, granulating ulcer, which eventually involved the entire nail-bed. The patient was admitted to Barnes Hospital in February, 1927. At this time, there were no palpable regional lymph nodes. A roentgenogram of the chest did not show any evidence of metastases. The roentgenogram of the thumb showed destruction of the bone in the distal phalanx. Further examination was negative. The lymphatic glands

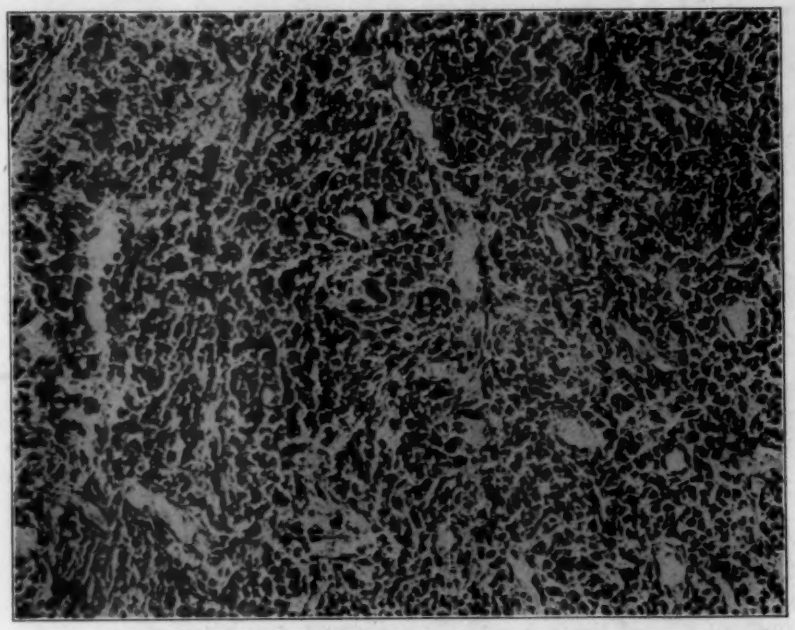

Fig. 4 (case 2).—Section showing both spindle and round cells with deeply staining nuclei; only a small amount of pigment and many small blood vessels are present.

Fig. 5 (case 3).—Coal-black tumor involving the bone of the distal phalanx; superficially, the growth was limited to the nail-bed.

of the axilla and the anticubital fossa were dissected out, and the thumb disarticulated together with the first metacarpal bone. The postoperative course was uneventful. There has not been any evidence of recurrence in the short time that has elapsed since the amputation.[6]

CASE 4.—A white woman, aged 68, had an incomplete history. The patient presented an extensive, black, fungating ulcer involving the entire finger nail-bed. The pathologic specimen was sent to this laboratory. Several large, black lymph glands were removed from the axilla in February, 1914. The patient has disappeared from observation and is presumably dead.

PATHOLOGY

Each of these patients presented a black, fungating ulcer involving the nail-bed. The ulcers, as a rule, were fairly well demarcated from the surrounding skin. It is an interesting fact that because of the black discoloration, two of the patients were first treated by other physicians for gangrene.

Microscopically, all of these cases showed two types of cells, probably representing different degrees of differentiation. The predominating cells were spindle shaped and grew in interlacing masses into the subcutaneous tissue down to the bone. The nuclei took a fairly deep stain. Mitoses were rare. Numerous areas of pigmented cells were interspersed throughout. The pigment was both intracellular and extracellular, and in several regions phagocytic cells containing pigment could be demonstrated. The other type of cell seen was polygonal or spherical and presented, relatively, many more mitoses. The nuclei were vesicular, with only a small amount of cytoplasm. Pigment was also found in these cells, but to a lesser extent than in the spindle-shaped cells.

The local lesion is limited by the fascial planes of the distal phalanx in a manner similar to that seen in infections. This phenomenon led Hutchinson to devise the term "melanotic whitlow." In many of the cases that have been reported by various observers, the lesion was first noted as a lentigo, or discoloration of the nail-bed. This may remain dormant for an extremely variable time. Subsequent extension is first by way of the regional lymphatics, metastases being first noted in the anticubital and axillary spaces before distant metastases are apparent.

PATHOGENESIS

The origin of melanotic tumors has been much discussed. The cell type has been considered epithelial, mesothelial and endothelial by different observers. The endothelial origin suggested by Reckling-

6. Since I sent the manuscript for this article to the publisher, the patient has returned with pulmonary and abdominal metastases and an enlarged gland in the posterior triangle of the neck.

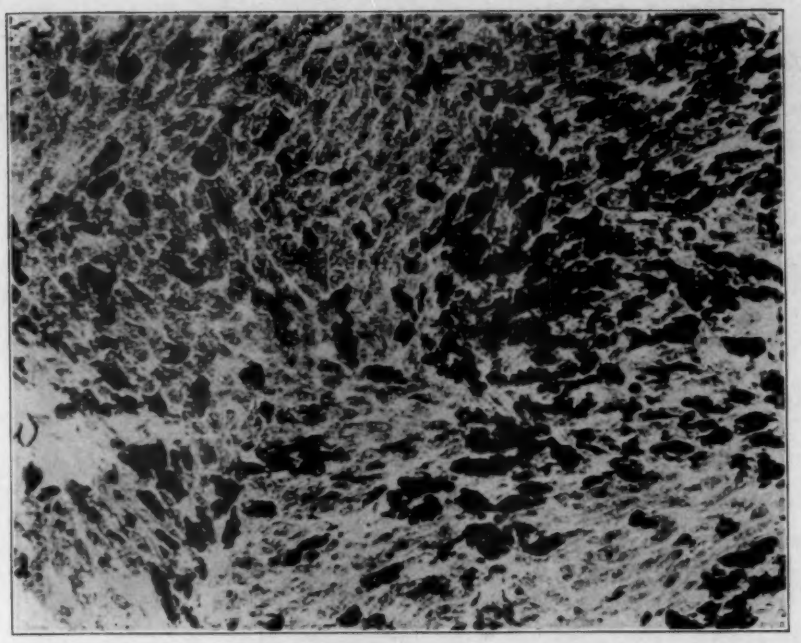

Fig. 6 (case 3).—Tumor composed almost entirely of spindle cells; abundant pigment and extracellular granules may be seen. In other areas, phagocytic cells with ingested pigment could be identified. There is little stroma present.

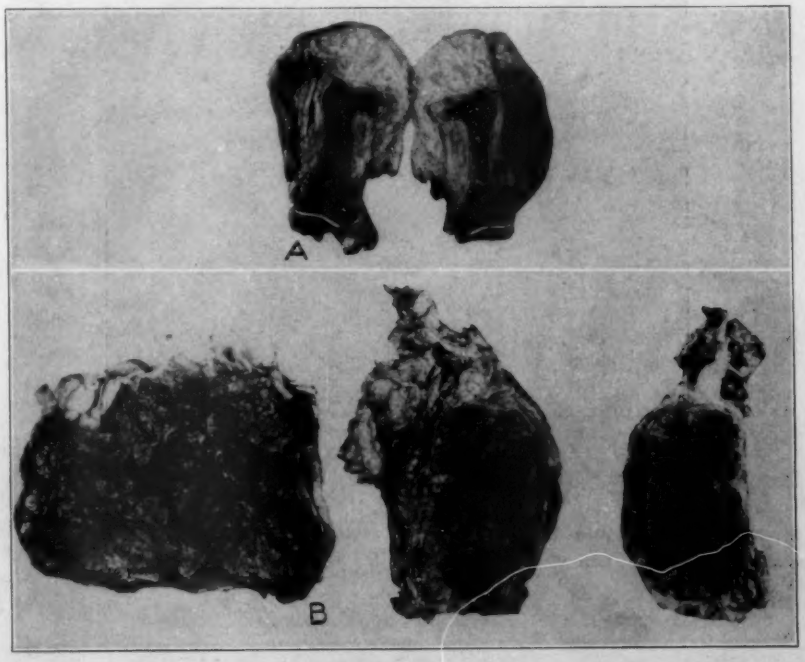

Fig. 7 (case 4).—*A*, the melanoma extending down to the periosteum and entirely limited to the region of the nail-bed; *B*, several large lymph glands removed from the axilla showing the gross pigmentation sometimes seen in metastases.

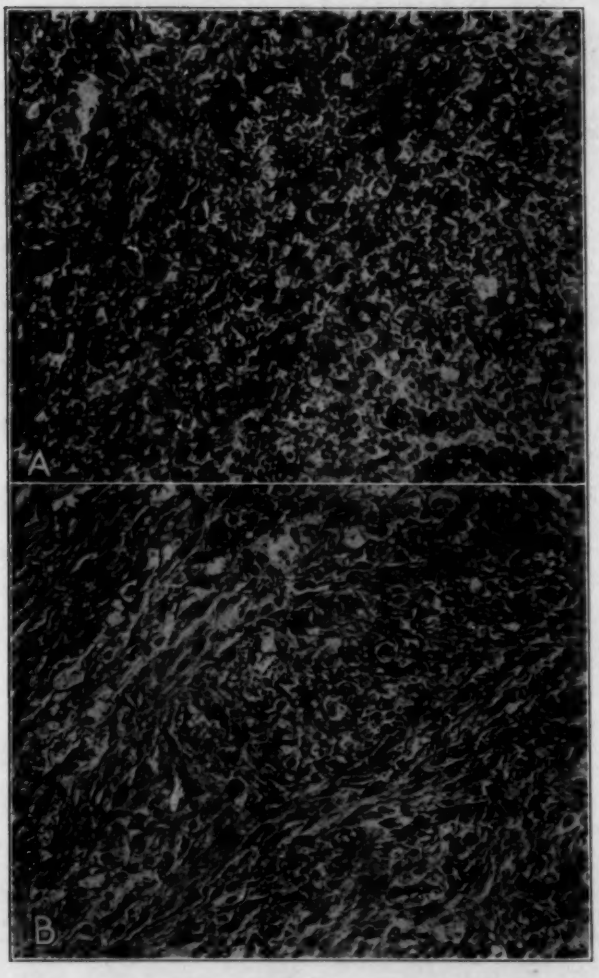

Fig. 8 (case 4).—*A* shows a section taken through the primary lesion. The cellular outline is obscured by the extracellular deposits of pigment. Many leukocytes may be seen. *B* shows a section taken through the metastasis to the axillary lymph nodes. No lymphatic tissue may be seen. Both round and spindle cells are present, a few of them containing pigment.

hausen has found little support. Unna insisted on an epithelial origin, while Ribbert championed that of mesothelium. The most conclusive studies, perhaps, are those of Bruno Bloch [7] and his associates. They have been able to demonstrate a melanin-producing ferment both in melanomas and in certain normal tissues by the use of 1 per cent solution of dioxyphenylalanine as a stain. This reaction has been termed the "dopa" reaction and the enzyme "dopa-oxydase." Melanin was the only pigment found in the skin. It was formed only by cells of ectodermal origin, i. e., the basal layer of the skin, cells forming the sheath and matrix of the hair, nevi, etc. In the corium, the cells forming true Mongolian spots gave a positive reaction. A negative reaction was obtained in the shaft of the hair, the chromatophores and the upper layers of the epidermis, especially the horny layers. Though melanin is often seen in chromatophores, it apparently is never formed there. Its presence is the result of phagocytosis of the melanin extruded by the epithelial cells; in other words, the "dopa" reaction, being dependent on the "dopa-oxydase," is positive only in those cells in which melanin is manufactured. Since it is positive only in cells of epithelial origin, with the exception of the blue Mongolian spots the cell origin of which is uncertain, such growths as nevi and melanomas have been considered epithelial by Bloch and his associates.

CLINICAL COURSE AND TREATMENT

Course.—Trauma is often associated with the tumor, and, peculiarly enough, many of the patients at first have been treated for infections. This is especially true of those lesions in which pigmentation was not marked in the beginning. When trauma has not occurred, the lesion appears at first as a discoloration in the lateral nail-bed, at times resembling a hematoma. Pain is not an important feature. As the lesion progresses, ulceration occurs and with it secondary infection, giving the appearance of a paronychia. Metastases are first noted in the anticubital and axillary spaces. The time of appearance of metastases is an extremely variable factor. In one of Jones' cases, axillary nodes were seen nine months after the initial lesion appeared, while in Boyer's case the initial lesion existed as a pigmented area for thirty years. After the appearance of axillary involvement, generalized metastases and death soon follow.

The tumor is more commonly seen in persons above the age of 40. The nail-beds of the fingers are more frequently involved than those of the toes, nearly half of the reported cases being in the thumb alone. Pigmentation appears to be a constant occurrence but may be difficult to detect in the early lesions first noted following trauma. Lesions have not been reported in the colored race.

7. Bloch, Bruno: Bull. Soc. franç. de dermat. et syph., 1921, p. 77.

Diagnosis.—A shallow, granulating ulcer in the nail-bed of a patient over the age of 40 should always be viewed with suspicion, especially if the ulcer does not tend to heal. This is true regardless of the history of the injury. The presence of pigment is pathognomonic. Any pigmentation in the nail-bed of a middle-aged patient should be carefully watched, whether or not ulceration is present.

Treatment and Prognosis.—The treatment consists of early amputation of the phalanx with dissection of the regional lymph nodes. Most of the patients who have been observed long enough have died from the disease; however, lymphatic dissections were made in few of these cases until after metastasis had occurred; in many, local currettings were frequently performed before amputation. Because of the variability of the time before metastases occur, one cannot but feel that early complete operation would accomplish better results. There is little evidence to indicate that radiation, in the form of either radium or the roentgen ray, is of much value.

CONCLUSIONS

1. Fifteen per cent of all melanomas at the Barnes Hospital were found to be subungual.

2. These tumors are probably of epithelial origin.

3. Pigmented ulceration occurring in the nail-bed of a patient above the age of 40 is a frequent occurrence.

4. Early amputation of the phalanx with dissection of the regional lymph node is advised.

CYSTS OF THE SEMILUNAR CARTILAGES OF THE KNEE*

ISADORE ZADEK, M.D.
AND
HENRY L. JAFFE, M.D.
NEW YORK

Recently we studied a case of cysts of the internal semilunar cartilage, which we believe contributes to the knowledge of the etiology and pathogenesis of this condition. Twenty-two cases of cysts of the semilunar cartilage have been reported since Ebner [1] described the first in 1904. Our case is the third reported case of cysts of the internal meniscus, the other two having been reported by Fisher [2] and by Allison and O'Connor.[3]

In the twenty-two cases, the patients' ages varied from 16 to 55, but most of them were in the third decade. Twenty patients were men, and three were women. There was a history of trauma immediately preceding the appearance of the cyst in nine cases, including ours; there was no history of trauma in five cases; in nine cases the presence or absence of trauma as a possible inciting factor was not mentioned.

REPORT OF CASES

History.—F. K., aged 39, wrenched the left knee slightly on Jan. 3, 1927, when he stepped out of an automobile. He experienced mild pain and disability immediately afterward and for about six weeks. A swelling then appeared and increased progressively. Concomitantly with the appearance of the swelling, the pain disappeared, and the patient was able to get about without difficulty, going up and down stairs and performing the work of a chauffeur. He came for treatment because the swelling was increasing, and was admitted to the service of Dr. Harry Finkelstein.

Physical Examination.—On March 23, 1927, the man was in excellent physical condition, and he walked without a limp. The one point of interest was the swelling on the left knee, which was the size of a hen's egg and was situated in the position of the internal semilunar cartilage, almost entirely superior to the line of the joint. The swelling was irregular and definitely fluctuating. It was not sensitive and was more prominent during extension than flexion of the knee.

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* From the Hospital for Joint Diseases.

1. Ebner, A.: München. med. Wchnschr. **51**:1737, 1904.

2. Fisher, A. G. T.: Internal Derangements of the Knee Joint, New York, The Macmillan Company, 1924.

3. Allison, N., and O'Connor, D. S.: Surg. Gynec. Obst. **42**:259, 1926.

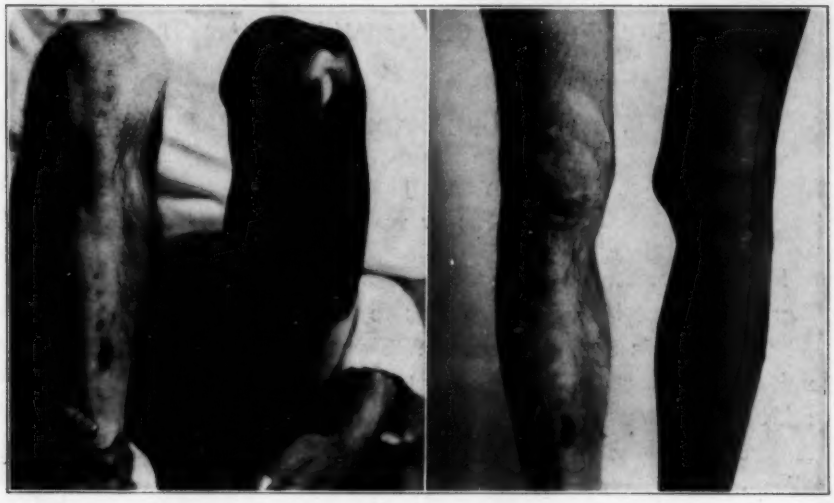

Fig. 1.—Photograph taken immediately before the operation, showing bulging of the internal aspect of the knee, most prominent on full extension.

Fig. 2.—This photograph shows almost the actual size of the cystic internal semilunar cartilage. The suture is taken through the posterior superior end of the cartilage.

Neither of these movements was limited. There were no signs of inflammation. The diagnosis of cysts of the internal semilunar cartilage of the left knee was made (fig. 1).

Operation.—An operation was performed on March 24, 1927, with the use of an Esmarch tourniquet. A 4-inch longitudinal incision was made directly over the swelling. The cyst presented directly beneath the deep fascia and was even

Fig. 3.—Markedly degenerated fibrocartilage. The cartilage is fragmented, and wide spaces appear. None of these spaces produced by the degeneration of the cartilage are lined by endothelium. This condition prevailed practically throughout the entire avascular portion of the cartilage.

larger than it had appeared on physical examination. It was multilocular, and its walls were thin in places. A considerable number of the cysts were ruptured during the operation. Almost the entire internal semilunar cartilage was removed with the cysts, which were most prominent at the midportion. They were

adherent to the capsule of the joint, and strands of fibrous tissue dipped down between them at some points. The cysts contained clear, thick, gelatinous material grossly identical with the material found in ganglions. A small portion of the capsule was removed with the cysts, and the deep structures were closed with chromic catgut. The skin was closed with silk, and a light plaster of Paris bandage was applied with the knee in full extension (fig. 2).

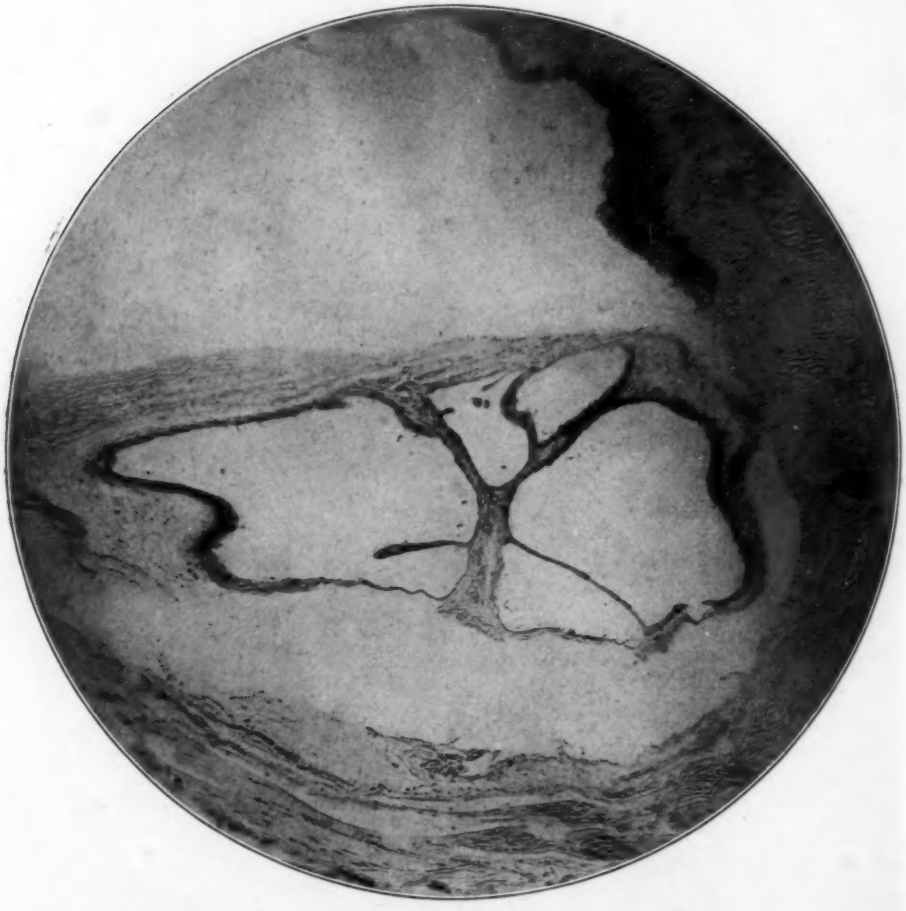

Fig. 4.—Multilocular cysts completely within the semilunar cartilage.

Gross Pathologic Observations.—The collapsed cystic left internal semilunar cartilage was roughly triangular when viewed from its upper surface. The cartilage measured about 6 cm. in length along its inner free border. The cystic area, which sprang from the outer vascular portion of the cartilage, was confined mostly to its middle third, though it extended for some distance anteriorly and posteriorly. The inner avascular fibrocartilage was consequently affected, being somewhat widened and thickened posteriorly and rather smaller

than the average through the region of the main cystic mass. On operative exposure, the main cystic mass was as large as a goose egg, but after removal it measured 4 by 3.5 by 1.5 cm., since some of the cysts had been perforated, and the fluid had escaped. When the semilunar cartilage was sectioned at right angles to its long axis, the posterior portion of the cartilage showed no cysts in the gross examination, and the cut surface appeared edematous and rather

Fig. 5.—A small cyst, lined by a synovial-like endothelium, completely within the semilunar cartilage.

translucent. The next section, made a little more anteriorly, showed a thickened semilunar cartilage with greenish, translucent, edematous and yellowish areas, the latter possibly areas of necrosis. The third section, cut still further anteriorly, showed an enlarged cartilage with a cyst measuring about 4 mm. in diameter within the middle of the outer vascular portion of the fibrocartilage. The fourth section, taken through the posterior border of the main cystic mass,

contained several small multilocular cysts within the substance of the cartilage surrounded by an edematous and, in some places, apparently necrotic cartilage. The inner avascular portion of the cartilage was thin. The next sections were made through the region of the largest cysts and showed collapsed cysts, some of which had been originally as much as 2 cm. in diameter. They were separated by white fibrous septums, the intracystic surfaces of which were smooth and

Fig. 6.—Small communicating synovial-lined cysts. The synovial endothelium is heaped up in one region.

shiny. These cysts communicated with each other, and as they extended laterally and upward they were applied to the internal lateral ligament and the capsule of the joint. With the accumulation of fluid, the walls had become thin. Only a fragment of noncystic semilunar cartilage remained attached to the cysts in this region. The last section, taken through the semilunar cartilage still further anterior to the main cystic mass, did not contain cysts.

Microscopic Examination.—In the first section the fibrocartilage was degenerated and fragmented, and wide spaces filled with fluid were produced, though these spaces might have been due partly to separation and shrinkage (fig. 3). Areas of necrotic fibrocartilage were seen, in which the nuclei and cytoplasm did not stain, and the nuclei in the fibrocartilage areas adjacent to them were swollen, giving the cells the appearance of hyaline cartilage cells with lacunae.

Fig. 7.—A cyst with irregular papillary projections covered with synovial endothelium. It was probably never completely distended.

More peripherally, the necrosis was less extensive, and the appearance of vascular fibrocartilage was resumed. The exposed upper surface of the cartilage in this region was covered by a layer of synovial membrane.

In the second section the cells of the cartilage of the free inner edge of the meniscus were swollen. Completely within the substance of this cartilage and occupying many low power fields was a large area of degeneration. There was

a gradual transition from the better preserved to the necrotic cartilage, the necrotic area was not encapsulated, nor was vascularization present in the avascular necrotic cartilage. Many new vessels had appeared in the outer vascular portion of the meniscus. As in the first section, true cysts were not seen.

In the third section, the first true cyst appeared. Practically all the avascular semilunar cartilage was necrotic. The nuclei and cytoplasm did not stain.

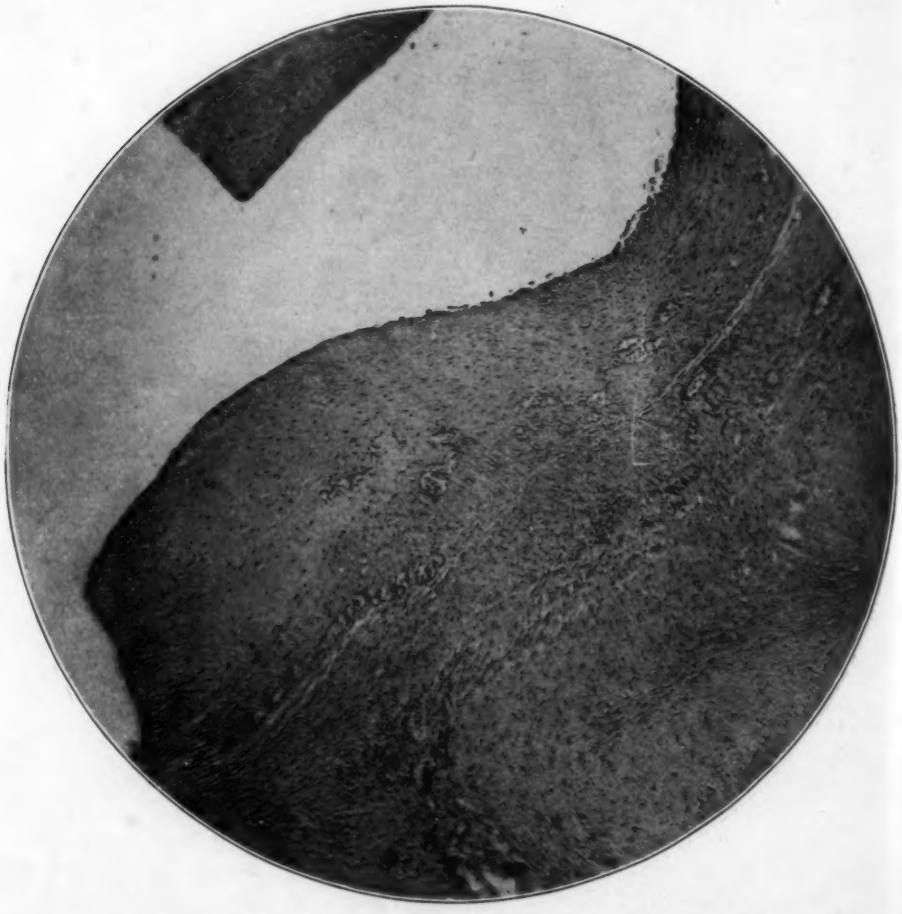

Fig. 8.—The connective tissue nature of the walls through the region of the largest cysts. Vessel formation is marked in the walls, but the synovial lining is not present.

Marked edema, vacuolization and space formation were present. In about the middle of the section a large cyst occupied two low power fields. It was lined by a membrane of flattened cells, two or three rows thick. Immediately beneath this lining layer was a narrow zone of fibrillar connective tissue. Vascular fibrocartilage completely surrounded the cyst and composed the rest of the section.

Another section, taken further anteriorly, showed one large cyst three low power fields in diameter and one smaller cyst. These cysts, which were lined by a synovial-like membrane, were in the outer vascular portion of the semilunar cartilage (fig. 4).

The fourth section also showed degeneration, edema and fragmentation of the inner portion of the semilunar cartilage. In the outer portion of the mensicus were many large and small communicating cysts lined by an endothelial layer resembling synovial membrane. In some of the smaller cysts papillary formations were present, covered by the synovial-like endothelium, as were also the fibrous septums which divided these cysts. In another section from this region the same changes were seen. The cysts were all within the enlarged outer vascular portion of the fibrocartilage and were completely surrounded by such cartilage (figs. 5, 6 and 7).

The fifth section, taken from the main cystic mass, showed large, irregular communicating cysts, some of which were from 10 to 12 low power fields in diameter. In places the linings of the cysts were flattened cells resembling connective tissue, but in other places the cells had become thickened and somewhat stratified, and the general appearance was more like that of synovial endothelium. Besides this endothelial layer, the wall of the cyst was composed of young connective tissue cells with abundant connective tissue fibrils. Some of the cyst walls contained granulation tissue with abundant lymphoid foci, but inflammatory changes were not present. Only a small fragment of semilunar cartilage was seen at the inner edge of the cysts. None of the large cysts which had expanded the capsule of the joint was surrounded by semilunar cartilage. In places the histologic appearance of the walls of the cyst through this area was similar to that of chronic synovitis, while in other regions it more closely resembled that of a ganglion (fig. 8).

The sixth section showed the same degenerative changes as those found in the inner portion of the semilunar cartilage. The outer vascular portion showed no cysts.

Summary of Pathologic Observations.—The semilunar cartilage was expanded and contained many cysts, which were an integral part of it. These cysts measured from a few millimeters to fully 2 cm. in diameter. All the smaller cysts were lined by a synovial-like layer and were completely surrounded by fibrocartilage. The larger cysts had expanded the capsule of the joint and had broken through the cartilage. In these the histologic appearance was more like that of a ganglion. Between the smaller cysts were papillary formations covered by synovial endothelium, which appeared to be undistended synovial inclusions. All the cysts seemed to have originated in the outer vascular portion of the semilunar cartilage, and the inner avascular portion showed extensive necrosis, but cysts had not developed in it.

COMMENT

Many theories concerning the origin of cysts of the semilunar cartilage have been advanced. According to the older German view,[4] these

4. Schmidt, E.: München. med. Wchnschr. **53**:1415, 1906. Riedel: Deutsche Ztschr. f. Chir. **132**:167, 1914. Eden: Naturwissenschaftliche medizinische Gesellschaft zu Jena, May 18, 1911.

cysts are ganglions that arise as the result of softening and colloid degeneration of para-articular, tendinous or periosteal tissues about the knee, owing to deficient nutrition following trauma. Phemister [5] also favors this idea, but does not believe in the primary vascular origin of the cysts or in the invariable association of trauma with the condition. He, like previous authors, did not find endothelium lining the cysts. The impression we gained from these papers was that the histologic studies were made only from the large cystic areas, which are, as we have shown, not entirely characteristic of the true nature of the cysts.

According to Fisher,[2] there is little doubt that these cysts are ganglions which originate in the tissues between the peripheral surface of the cartilage and the synovial membrane which covers it at this spot. Mucoid degeneration of the connective tissue takes place, in which the fibrocartilage at the periphery of the meniscus may participate.

The view maintained by Jean,[6] Allison and O'Connor [3] and Kleinberg [7] is that the cysts represent the end-results of a degenerative process in the cartilage. According to Allison and O'Connor, a nonlacerating injury interferes with the blood supply to the cartilage and finally results in degeneration and formation of cysts. Kleinberg is in accord with this view.

Ollerenshaw [8] was the first to find a flattened endothelium, similar to synovial membrane endothelium, lining the cysts. On the basis of this observation, he opposed the idea of degeneration cysts or of cysts following hemorrhage, and advanced the conception of their developmental origin. He believed that small endothelial nests, included in the cartilage during its development, began to secrete and became distended following trauma. Kleinberg also reported endothelium lining some of the cysts, but he believed it to be of lymphatic origin.

In our case there was no doubt about the synovial nature of the lining endothelium. Such a lining layer was found in all the smaller cysts. The larger cysts were lined in places by flattened cells which might possibly have been fibroblasts, but which were probably flattened endothelial cells because they showed gradual transitions to this type. We cannot say definitely whether these cysts resulted from congenital

5. Phemister, D. B.: Cysts of External Semilunar Cartilage of Knee, J. A. M. A. **80**:593 (March 3) 1923.

6. Jean, G.: Bull. et mém. Soc. nat. de chir. **1**:775, 1924.

7. Kleinberg, S. J.: Bone & Joint Surg. **9**:323, 1927.

8. Ollerenshaw, R.: Brit. J. Surg. **8**:409, 1921.

synovial inclusions, or whether they were formed in later life through invasion of the meniscus by synovial membrane following tearing of the outer portion of the cartilage where it fuses with the joint capsule. The latter consideration would seem improbable, as there is no history of injury in many of the cases.

Certain features in our case favor the congenital origin of these cysts. These are the multiplicity of the cysts, the presence of papillary synovial inclusions without formation of cysts, and the absence of recent or old hemorrhage into the cysts, our patient having been operated on within two months after trauma. The synovial tissue may become included during embryonic life, since the semilunar cartilages are developed in folds of synovial membrane derived from the interchondral disk. Perhaps the inclusion occurs when the vessels penetrate the outer portion of the meniscus.

It is difficult to evaluate the part that trauma plays in the development of these cysts. About half of the cases have recorded histories of trauma followed by formation of a cyst within a few months. Trauma probably leads to a rapid filling up of preformed congenital cysts. We find no evidence to support the view which may present itself that the cysts are formed following tearing of the meniscus and the consequent invasion by synovial membrane.

The view that the cysts follow degenerative changes in the cartilage cannot be accepted, because cysts of the semilunar cartilage are true cysts. In our specimen, the fibrocartilage was degenerated, especially the inner avascular portion. Large areas were absorbed; in other regions there was wide separation of the tissues, but nowhere in the degenerated cartilage was true cyst formation seen, as demonstrated by the presence of a cyst lining. The degenerative changes were secondary, caused by the pressure exerted on the cartilage during the process of enlargement of the cysts.

The presence of a synovial endothelial lining in the small and medium-sized cysts refutes the idea that the cysts are ganglions or that they arise as the result of degeneration of the tissues between the cartilage and the capsule of the joint. We believe that endothelial linings have not been reported more frequently because the histologic preparations were made mostly through the region of the large cysts. We agree with Ollerenshaw's view that the lesion is a true cystic condition of the semilunar cartilage and that it is most likely congenital in origin.

As to why the cysts occur so much more frequently in the external than in the internal cartilage, we, like the others, cannot explain. However, when more cases are recorded, this difference may be found to be purely accidental.

CONCLUSIONS

1. We report a case of cysts of the internal semilunar cartilage in a young man, in whom the condition became apparent several weeks after he had wrenched the knee.

2. This is the third reported case of cysts of the internal meniscus.

3. Cysts of the semilunar cartilage are true cysts and are lined by a synovial-like endothelium.

4. We believe that the cysts are probably congenital in origin.

5. Trauma is present in about half the cases and is only an initiating factor which leads to a rapid filling up of the preformed cysts with secretion.

6. Cysts of the semilunar cartilage are more prominent during extension than during flexion. During flexion they can extend further into the knee joint, because more room is made for them, and the capsule to which they are adherent peripherally is taut.

ACUTE TRAUMATIC ULCERS OF THE SMALL INTESTINE

OBSERVATIONS ON THE EFFECTS OF APPLICATION OF CLAMPS ON THE GASTRO-INTESTINAL TRACT: AN EXPERIMENTAL STUDY *

WILLIAM JOHN GALLAGHER, M.D.
CHICAGO

It is generally recognized that trauma may be an important contributing factor in the genesis of chronic peptic ulcer. However, opinions differ regarding the influence of clamps as a source of trauma in gastro-intestinal operations and the relation of this form of trauma to chronic jejunal and experimental ulcers. A study of this problem was undertaken that more definite knowledge might be obtained of the nature and extent of the injury produced by clamps. The questions that I have endeavored to answer are: Do acute ulcers occur from pressure, and if so, do these ulcers become chronic? What is the influence of the nutritional state of the animal on the production and healing of these lesions? What is the effect of injury from clamps on those parts of the intestinal tract free from peptic activity?

LITERATURE

The first postoperative jejunal ulcer was reported by Braun [1] in 1899. Since then many such ulcers have been observed. The occurrence of jejunal ulcer varies with the pathologic condition in the stomach or duodenum, the type of operation and the surgeon. It occurs most commonly following gastro-enterostomy. Haberer [2] reported ulcers in 17 per cent of seventy-one patients, while in an analysis of 6,214 gastro-enterostomies at the Mayo Clinic, Verbrugge [3] noted ulcers in 1.41 per cent; more recently Lewisohn [4] found ulcers in 34 per cent of ninety-two patients. In a review of the literature,

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* From the Seymour Coman Fellowship in the Department of Physiology of the University of Chicago, and the Department of Surgery of Rush Medical College of the University of Chicago.

1. Braun, H.: Demonstration eines Präparates einer 11 monate nach der Ausfuhrung der Gastro-Enterostomie entstandenen Perforation des Jejunum, Arch. f. klin. Chir. **59**:157, 1899.

2. Haberer: Zur Frage des Ulcus pepticum jejuni auf Grund alterer und neurer klinischer Erfahrungen, Arch. f. klin. Chir. **119**:712, 1922.

3. Verbrugge, Jean: Gastro-jejunocolic Fistula, Collected Papers of the Mayo Clinic **16**:104, 1924.

4. Lewisohn, R.: The Frequency of Gastro-jejunal Ulcer, Surg. Gynec. Obst. **40**:70, 1925.

Moynihan [5] gives the time of occurrence of the ulcers after operation as from ten days to ten years, with the largest number of patients showing symptoms within the first year.

Most authors consider a high degree of hydrochloric acid and operative trauma as the important cause of jejunal ulcer. In a report of 309 postoperative jejunal ulcers, Erchenbrecht [6] was of the opinion that there was a primary injury of the jejunal wall from operative trauma and further corrosion by gastric juice, while Haberer and Denk [7] have found ulcers in the line of the clamp of previous operations. They state that the mechanical factors are most important, and that the more difficult the gastro-enterostomy the more frequent is the occurrence of postoperative jejunal ulcer.

After an extensive study of 170 resected ulcers, Orator [8] concluded that inflammation of the jejunum following gastro-enterostomy was secondary in jejunal ulcer; that in addition to an unknown factor of general character in the stomach, there was a hyperplasia of the mucous membrane of the fundus; and that when the element of trauma due to clamps or too small an opening was added, chronic jejunal ulcer resulted.

According to Kausch,[9] the amount of compression from clamps that caused injury to the mucosa was always a variable factor. He believed that the difference in the technic of the various surgeons probably explained the apparent geographic distribution of chronic jejunal ulcer in Germany and in Austria. Many authors (Roeder,[10] Konjetzny,[11] Pauchet,[12] Woolsey [13] and Terry [14]) have observed ulcers in the line of the clamp of previous operations and have considered this form of trauma as an important contributing cause.

5. Moynihan, B.: Jejunal Ulcer, Abdominal Operations, ed. 4, Philadelphia, W. B. Saunders Company, 1926, p. 288.

6. Erchenbrecht, H. P.: Ein Beitrag zur Kasuistik des Ulcus pepticum jejuni postoperativum, Beitr. z. klin. Chir. **127**:365, 1922.

7. Haberer and Denk, cited by Kausch, footnote 9, ninth reference.

8. Orator, V.: Beitr. zur Magenpathologie (histologische Untersuchungen an klinischen Resktionsmaterial) Virchows Arch. f. path. Anat. **255**:637, 1925.

9. Kausch, W.: Das Ulcus pepticum, Handbuch der Praktischen Chir. **3**:289, 1923.

10. Roeder, C. A.: The Relation of Surgical Technic to Gastro-Jejunal Ulcer, Arch. Surg. **3**:622 (Nov.) 1921.

11. Konjetzny, G. E.: Entzündliche Genese des Magen-Duodenal-gechwürs. Ein Beitrag zur Kenntnis der Ätiologie, Pathogenese, und Therapie Magenduodenal geschwürs, Arch. f. Verdauungskr. **36**:189 (Dec.) 1925.

12. Pauchet, V.: Ulcus jéjunal post-operatoire, Bull. Acad. de méd., Paris **83**:527 (June) 1920.

13. Woolsey, J. H.: Gastro-Jejunal and Jejunal Ulcer, Cause, Diagnosis and Treatment, S. Clin. N. Amer. **3**:657 (June) 1923.

14. Terry, W. I.: Ulcer of the Jejunum following Gastro-Enterostomy, J. A. M. A. **75**:219 (July 29) 1920.

The most direct evidence of injury to the jejunal mucosa from clamps has been given by Coffey.[15] A patient, on whom he had performed a posterior gastro-enterostomy for ulcer, died from hemorrhage fifty-six hours after the operation. The operation was performed in thirty minutes. Autopsy revealed an acute lesion in the line of the clamp with erosion of a blood vessel. Coffey has also observed similar injuries of the mucosa of experimental animals which were operated on.

Ivy [16] and others have reported that chronic peptic ulcer is rarely seen in the experimental animal. He found only two chronic ulcers at postmortem examinations on 850 dogs; one in an animal from which the thyroid and parathyroid had been removed, and the other in an animal in which the pancreatic duct had been ligated.

Mann and Williamson [17] produced chronic jejunal ulcers in 90 per cent of the dogs on which they experimented by an extensive operative drainage of the duodenum into the ileum. More recently, Morton [18] repeated this work and obtained chronic ulcers in 100 per cent of the animals, in which, he states, the operative work was done without the use of rubber-covered clamps. Ivy's [19] contention is that trauma and the poor physical condition of the animals are important predisposing factors in chronic experimental ulcer. By keeping up a good state of nutrition, he obtained only a small number of ulcers, and when clamps were eliminated and a Polya operation performed, no ulcers resulted. In my laboratory experiments,[20] 30 per cent of the chronic jejunal ulcers were produced when Polya operation was performed with clamps and the animals were in a poor physical condition. Healthy jejunal mucosa is indifferent to gastric secretions in dogs, according to Dogliotti and Riccio.[21] They were unable to produce ulcers in dogs when the operations were done without unnecessary traction or injury to the tissues. There are, however, no recorded observations of the appearance of the mucosa in the line of the clamp soon after operation. The presence of a chronic ulcer from one to two months later is indirect proof of a possible original operative injury to the intestinal wall.

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15. Coffey, R. C.: A Plea for More Direct Methods in Dealing with Gastric Ulcers and Cancers, J. A. M. A. **57**:1034 (Sept. 23) 1911.

16. Ivy, A. C.: Contributions to the Physiology of the Stomach, Arch. Int. Med. **25**:6 (Jan.) 1920.

17. Mann, F. C., and Williamson, C. S.: The Experimental Production of Peptic Ulcer, Ann. Surg. **77**:409, 1923.

18. Morton, C. B.: Observations on Peptic Ulcer, Ann. Surg. **85**:207 (Feb.) 1927.

19. Ivy, A. C.: Personal communication to the author.

20. Gallagher, W. J., and Mullen, B. P.: Gastric Ulcer Studies, unpublished.

21. Dogliotti, A. M., and Riccio, F.: Jejunal Ulcer After Gastro-Enterostomy, Arch. Ital. di Chir. **10**:821 (Dec.) 1924.

EXPERIMENTAL WORK

Technic.—Normal, medium sized, healthy dogs were used. After two or three operations on the same animal, some emaciation, cachexia and infection of the skin were usually present. Ether anesthesia and aseptic technic were used in all operative work. Rubber-covered stomach clamps were employed in some of the experiments. In most cases, Young's tongue clamps were used. They have smaller blades, and consist of two soft, corrugated rubber pads, 2 by 1 by 0.4 cm., held in two elliptical shaped, thin, metal rings at a distance of 3 mm. from the point of application to the bowel (fig. 1). These clamps are more easily applied with less unnecessary trauma. It was thought the corrugations in the rubber pads of the clamps might prevent uniform pressure. The use of smooth pads made no perceptible difference in the results.

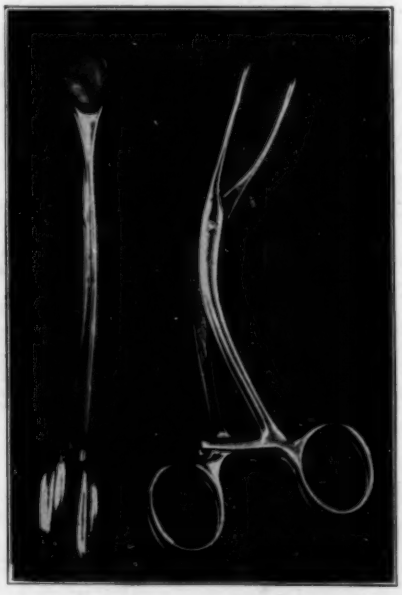

Fig. 1.—Young's tongue clamps used in pressure experiments on the bowel.

Clamps were applied to the sites of most frequent occurrence of chronic ulcers in the stomach, duodenum and jejunum, and to other parts of the jejunum, ileum and colon for comparison. The time of application was carefully observed. The shortest time a clamp was applied was fifteen minutes, while the longest was one hour and twenty-five minutes. In addition, the length of time of the return of circulation to the clamped area was noted in all cases.

The third important factor in regard to the use of a clamp was the amount of pressure used. An accurate method of measuring this pressure was attempted through experiments with an instrument devised by Dr. A. J. Carlson, which will be discussed later. The bowel was not clamped tightly; only sufficient pressure to produce local blanching was applied. This was assumed to represent the pressure necessary to secure hemostasis in operations on the gastro-intestinal tract (in an animal to be killed an incision was made through such a blanched area of the wall of the bowel; only a slight amount of oozing occurred). Hemostasis or a local anemia was produced by the pressures applied.

In some of the experiments, two superficially, loosely tied silk sutures, 1 cm. on either side of the clamp, were inserted as markers.

Following operation, the animals were placed on an ordinary laboratory diet of bread, meat and water. There was marked disturbance of nutrition, particularly following trauma to the duodenum. No attempt was made to keep the animal in a good state of nutrition, since it was desired to know the influence of a poor physical condition on the production and healing of traumatic lesions of the gastro-intestinal tract.

Twenty animals were studied. In most cases, from two to four experiments were performed on each animal at various times. For the sake of clearness and brevity, the experiments will be divided into four groups. In the first group the amount of pressure necessary that produced blanching of the intestine was observed in ten animals. In the second group, clamps were applied to the walls of the stomach and duodenum of ten dogs. Usually two clamps were applied on different areas at the same time. In the third group, the major pancreatic duct was ligated at the same time clamps were put on the stomach and duodenum. In the fourth group the application of clamps was carried out on the lower jejunum, ileum and colon.

Histologic studies were made of most acute lesions and of those areas which had healed.

Gastric analyses were made on three of the animals in group 2 before and after the clamps were applied. The dogs were given 200 cc. of meat juice and a slice of bread. After from thirty-five to fifty minutes, aspirations of the stomach were made without an anesthetic.

Measurement of Pressure in Millimeters of Mercury Necessary to Produce Local Blanching in the Wall of the Intestines and in the Stomach.—An instrument devised by Dr. A. J. Carlson was used (fig. 2). The apparatus consists of a rectangular metal platform, in one end of which is an upright steel rod, which holds a glass tube of desired length with an 8 mm. bore. The lower end of the tube is covered with a rubber diaphragm. On the side of the glass tube is an extension to which is attached rubber tubing with a glass funnel; by raising or lowering this intake, the height of the column of mercury can readily be varied. An adjustable millimeter ruler is attached to the side of the glass tube. The platform was set over the abdominal incision and a loop of bowel or stomach placed on the platform. The glass tube was then lowered to the margin of the bowel. By elevating the intake the mercury was increased, distending the rubber diaphragm which exerted pressure on the wall of the bowel. When blanching appeared, the intake was lowered until the normal color returned. By repeating this procedure, the blanching point was again observed and recorded.

Even with the greatest care and by observing closely all factors, it was noted that the readings varied greatly, not only in different parts of the gastro-intestinal tract, but also in the same part at varied intervals and under different degrees of anesthesia and intestinal activity.

The experiments were performed on ten dogs, three of which were killed the next day for examination of the mucosa after varied pressures of mercury had been applied for from thirty-eight to forty minutes. The remaining seven animals were used in subsequent applications of clamps.

The capillary pressure, taken at the base of the finger-nail in two persons, was found to be 51 and 54 mm. of mercury with this instrument. Von Recklinghausen,[22] by a different instrument gives 55 mm.

22. Von Recklinghausen, cited by Howell, W. H.: Textbook of Physiology, ed. 6, Philadelphia, Saunders, 1918, p. 499.

of mercury as the capillary pressure in man at the base of the finger-nail, while Danzer and Hooker,[23] by a more accurate apparatus, gives an average of 22.2 mm.

RESULTS OF EXPERIMENTAL WORK

GROUP 1.—The local blanching pressures in ten dogs were observed to vary on the different parts of the gastro-intestinal tract with the degree of anesthesia and the activity of the animal. The difference in

Fig. 2.—Instrument used for measuring anemia pressures of the bowel in millimeters of mercury, with a loop of duodenum on the platform.

pressure is probably explained by the difference in the anatomy and the physiology of the various portions.

In dogs 18, 19 and 20, pressures in millimeters of mercury were applied to the walls of the duodenum for from thirty-eight to forty minutes, and the animals were killed the next day. There were no gross changes in the mucosa when pressure was less than that necessary

23. Danzer, C. S., and Hooker, D. R.: Capillary Blood Pressure in Man, Am. J. Physiol. **52**:136, 1920.

to produce local anemia. For example, when the blanching pressure of 150 mm. of mercury was applied for forty minutes in dog 19, two superficial circular areas of necrosis of the mucous membrane were found twenty-four hours later.

As the readings of capillary pressure obtained at the base of the nail in two persons were approximately the same as those found by other observers with different instruments, the high figures obtained for blanching on the bowel is partly explained by the anatomy and physiology of the different parts. Two factors of importance are: 1. The intestinal lumen must be collapsed, that is, just sufficient pressure must be exerted to bring the walls together to obtain the zero point.

TABLE 1.—*Synopsis of Experiments of Mercury Readings on Ten Dogs in Group 1. (The Figures Indicate Millimeters of Mercury Required to Produce Anemia)*

Dog	Date	Stomach	Duodenum	Jejunum	Colon	Time Applied	Results	Remarks
5	11/30/26	...	175	170	160	.....	.....	Light anesthesia
8	12/10/26	...	145	140	150	.....	.....	Deep anesthesia
10	12/14/26	...	155	150	...	.....	.....	Deep anesthesia
12	12/17/26	...	157	155	...	.....	.....	Deep anesthesia
14	12/23/26	161	150	140	...	.....	.....	Deep anesthesia
16	1/20/27	190	160	153	150	.....	.....	Light anesthesia
17	2/ 7/27	170	184 175	175 155	...	.....	.....	Light and deep anesthesia
18	2/ 8/27	...	160	...	...	100 mg. of mercury to duodenum for 40 minutes	Normal mucosa	Anemia not produced with 100 mm. of mercury
19	2/ 9/27	...	150	...	...	150 mm. of mercury for 40 minutes	Superficial erosions 4 by 3 mm. of duodental mucosa	Anemia produced with 150 mm. of mercury
20	2/ 9/27	...	150	...	...	75 mm. of mercury for 38 minutes	Normal mucosa	Blanching not observed with 75 mm. of mercury

2. The intestine must be comparatively free from activity. The presence of peristalsis will cause blanching. The resistance of the rubber diaphragm holding the column of mercury will also add a certain amount of error.

The figures obtained approximate those given by Dawson [24] and Burton-Opitz [25] for blood pressures in the large arteries of dogs. They have found the blood pressure of dogs to vary from 104 to 172 mm of mercury under various conditions. The readings, though high, are fairly constant for each animal and are not intended to represent capillary pressures in the intestinal wall, but the pressures in millimeters of mercury necessary to produce grossly visible blanching as observed when clamps are applied. They are approximately the pressures used in the experiments with clamps.

24. Dawson, cited by Howell (footnote 23).
25. Burton-Opitz, cited by Howell (footnote 23).

Experiments on Three Dogs with Acute Duodenal Lesions.—The animals studied and the method of study are inadequate for a proper appreciation of the motor or secretory activity of the stomach. It was always difficult to get the animal to eat for several days after trauma to the duodenum.

In the three animals that were studied, a delay in the emptying time of the stomach was not observed. The amount of free acid in dog 1 was decreased below that observed preoperatively, while in dog 2 and 3, there was a low degree of free acid to begin with, and an apparent increase in the acidity following trauma to the duodenum.

Dragstedt and Vaughn,[26] observed in dogs with experimental pyloric ulcer and Pawlow pouches that there was an increase in gastric acidity when the acid secretion was abnormally low to begin with. Ivy [27] has observed a delay in the emptying time of the stomach in animals that

TABLE 2.—*Gastric Analyses on Three Dogs with Acute Duodenal Lesions*

Dog	Date	Pre-operative Days	Post-operative Days	Quantity, Cc.	Free Acid Units	Total Acid Units	Time of Collection, Minutes
1	11/22/26	1	..	20	50	73	35
	11/30/26	..	7	0	0	0	35
	12/ 9/26	..	16	20	14	65	45
	12/13/26	..	20	1	0	14	45
2	11/23/26	1	..	57	3	25	45
	12/ 8/26	..	14	2	5	15	35
	12/ 9/26	..	15	22	13	40	50
	12/13/26	..	19	5	8	14	40
3	11/28/26	1	..	30	4	60	65
	12/ 8/26	..	9	4	10	72.5	40
	12/ 9/26	..	10	15	20	43	50
	12/13/26	..	14	18	48	41	40

had acute ulcer of the duodenum. This was not present in the three animals studied.

Bogendörfer,[28] in experiments on dogs, found that lesions of the mucous membrane of the small intestine caused a decrease in the secretion of hydrochloric acid in the stomach. In dog 1 this was found to be true, when the acidity was high preoperatively.

Ivy [29] states that two factors are necessary for chronic ulcer in the dog, (1) a temporary lowered body resistance, and (2) a temporary pathologic mucous membrane manifested by hypoacidity or achylia. Because of this view and Bogendörfer's [28] observations, a study of

26. Dragstedt, L. R., and Vaughn, A. M.: Gastric Ulcer Studies, Arch. Surg. **8**:791 (May) 1924.

27. Ivy, A. C.: Experimental Studies on Gastric and Duodenal Ulcer, Am. J. Physiol. **49**:143, 1919.

28. Bogendörfer, L.: Beziehungen zwischen Magensaftsekretion und Dünndarm, Arch. f. Verdauungskr. **39**:99 (Oct.) 1926.

29. Ivy, A. C.: Studies on Gastric and Duodenal Ulcer, J. A. M. A. **75**:1540 (Dec. 4) 1920.

the gastric secretion in animals with acute traumatic lesions of the duodenum was attempted. The amount of material studied, however, is too small to permit of any definite conclusions.

RESULTS OF EXPERIMENTS IN GROUP 2

GROUP 2.—In the ten animals of this group it was found that no gross defects of the gastric mucosa were produced by the clamps and only a slight superficial roughness when they were applied for an

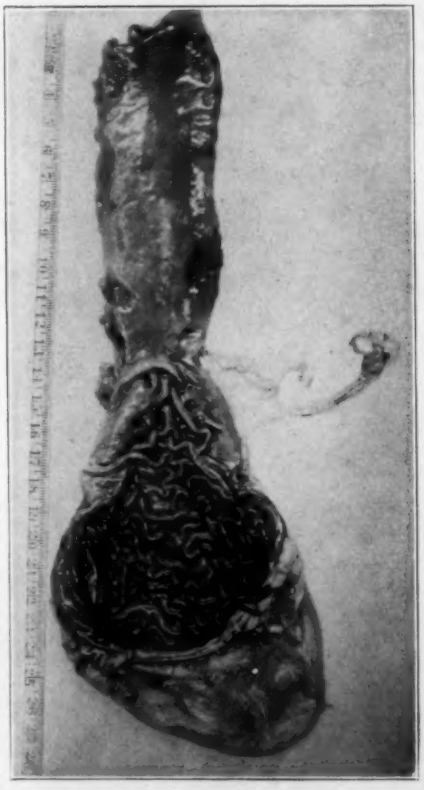

Fig. 3 (dog 3, group 2).—Two acute ulcers of the duodenum seven days after pressure had been applied for one hour.

hour or more. Microscopically, however, scar tissue was observed principally in the serosa and muscularis from forty-eight to sixty-two days later. In the duodenum, acute ulcers occurred in the mucosa when slight blanching was produced for thirty-two minutes; complete sloughing of the area blanched by clamps occurred when pressures were maintained over fifty minutes, leaving typical punched-out, acute, perforating ulcers. Larger areas of the wall of the bowel were traumatized by rubber-covered stomach clamps than by Young's clamps.

Fig. 4.—Photomicrograph of ulcers in figure 3. Note perforation of ulcer; × 60.

Fig. 5.—Photomicrograph of margin of ulcer in figure 3. Marked proliferation of mucosa with exudate in submucosa; × 60.

TABLE 3 (group 2).—*Synopsis of the Protocols of Ten Healthy Dogs with Acute and Healed Lesions of Stomach and Duodenum, Produced by Pressure*

Experiment	Date	Operation	Duration, Minutes	Return of Circulation, Seconds	Necropsy: Interval, Days	Necropsy: Results and Remarks	Necropsy: Histologic Studies
1*	11/23/26	Young's clamp applied to stomach 3 cm. from pylorus, lesser curvature and duodenum, 2 cm. from pylorus	40	5	48	Emaciated; no gross changes in mucosa of stomach or duodenum; died fifth day after second application of clamp	Stomach: scar tissue of serosa and muscularis, round cells in submucosa; duodenum: mucosa healed, leukocytic infiltration in mucosa and submucosa; round cells in submucosa; hyperplasia of Brunner's glands
2	11/24/26	Young's clamp applied to stomach 6 cm. from pylorus, lesser curvature and duodenum, 2 cm. from pylorus	50	8	40	Fundus of gallbladder adherent to clamped area of duodenum; puckered scar of duodenal mucosa; gastric mucosa negative	Gastric mucosa normal; duodenum: scar tissue of serosa, muscularis and submucosa with round cells; atrophy superficially of mucosa
3	11/26/26	Young's clamp applied to stomach 4 cm. from pylorus, lesser curvature and duodenum, 2 cm. from pylorus, anterior wall	60	10	7	Stomach: slight roughness of mucosa 1 by 1 cm.; duodenum: two acute ulcers of mucosa, 1.5 by 1 cm. and 0.2 cm. deep; food in stomach eaten 24 hours previously	Superficial erosion of gastric mucosa with some leukocytic infiltration in submucosa; duodenum: perforating ulcers, proliferation of mucosa at margin, base formed by serosa
4	11/29/26	Young's clamp applied to stomach 4 cm. from pylorus, lesser curvature and duodenum, 1.5 cm. from pylorus, anterior wall	65	20	48	Adhesions to stomach and duodenum; margin of liver adherent to duodenum at site of clamp, where wall is thin and dilated 1.5 by 1 cm.; puckered scar of mucosa 1 by 0.4 cm.	Gastric mucosa normal; duodenum: scar tissue in mucosa, submucosa, muscularis and serosa; desquamation of surface epithelium of mucosa; atrophic changes in Brunner's glands
5	11/30/26	Young's clamp applied to stomach 4 cm. from pylorus, lesser curvature and duodenum, 1.5 cm. from pylorus, anterior wall	80	25	60	Adhesions to clamped areas of stomach and duodenum; slight dilatation of clamped area of duodenum with puckered scars 1.2 by 1 cm. and 0.8 by 0.4 cm.	Scar tissue and round cells in all layers of clamped area of stomach; duodenum: superficial erosions of mucosa, some leukocytic infiltration; round cells in muscularis and submucosa
6	1/29/27	Young's clamp applied to duodenum 4 cm. from pylorus, anterior wall	15	Instantly	2¼	No gross change of duodenal mucosa	Superficial erosion of mucosa of duodenum, leukocytic infiltration of mucosa, submucosa and muscularis; no changes in tissue 1 cm. from this area
7	12/ 2/26	Young's clamp applied to stomach 2 cm. from pylorus, lesser curvature and duodenum, 2 cm. from pylorus, anterior wall	85	30	5	Slight roughening of gastric mucosa 1 by 1 cm.; two acute perforating ulcers of duodenum, 1.5 by 0.3 cm., sharp margins	Gastric mucosa, superficial erosion and slight exudate; duodenal ulcers, slight exudate in margins, base formed by serosa; proliferation of mucosa at margin
8†	12/ 8/26	Stomach clamps applied to stomach 4 cm. from pylorus, mid-portion, and to duodenum 2 cm. from pylorus, anterior wall	45	10	68	Adhesions of stomach and duodenum; slight dilatation and thinning of wall of duodenum at site of clamp, puckered scar mucosa	Gastric mucosa normal; duodenum: scar tissue in mucosa, submucosa, muscularis and serosa, and inclusion of mucosa tubules in muscularis and submucosa
9‡	12/10/26	Stomach clamps applied to stomach 1 cm. from pylorus and duodenum, 1 cm. from pylorus, anterior wall	50	10	45	Adhesions to clamped area of stomach and duodenum at site of clamps; slight dilation of duodenal wall at site of clamp; no gross changes of mucosa of stomach or duodenum	Gastric mucosa normal; scar tissue changes in mucosa, submucosa and muscularis of duodenum
10	12/13/26	Stomach clamps applied to stomach 1 cm. from pylorus and duodenum, 1 cm. from pylorus, anterior wall	60	20	3	No adhesions or infection present; considerable blood in stomach and small intestines; sloughing of mucosa in line of clamp of duodenum 4.5 by 0.4 by 0.2 cm.	Gastric mucosa normal; duodenum: leukocytic infiltration of submucosa and muscularis, complete sloughing of mucosa; proliferation of mucosa at margin of lesion
11	1/26/27	Young's clamp applied to duodenum, anterior wall, 4 cm. from pylorus	32	Instantly	1	Duodenum normal externally; superficial necrosis of mucosa of duodenum at site of clamp 1.5 by 0.8 cm. and 0.1 cm. deep; sharp margin; base covered with fibrin	Superficial necrosis and sloughing of mucosa, with exudation, hemorrhage and dilatation of glandular structures to basement membrane; some exudate of submucosa and muscularis

* Exploratory on forty-third day; omentum adherent to clamped areas of stomach and duodenum; no palpable defect in mucosa.
† Exploratory on forty-ninth day; adhesions between liver, stomach and duodenum; no defects in mucosa.
‡ Passed blood in stools; died from intestinal hemorrhage on the third day.

Acute intestinal hemorrhage and death occurred in one animal on the third day from injury to the mucosa of the duodenum when rubber-covered stomach clamps had been used. Gross injury to the duodenal mucosa was not observed when clamps were applied for fifteen minutes; microscopically, exudate, cellular infiltration and superficial necrosis of the mucous membrane were noted after twenty-four hours. In one animal with an acute duodenal ulcer, a gastric retention of twenty-four hours was observed on the seventh day. The animals were always

Fig. 6 (experiment 7, group 2).—Acute perforating ulcers of the duodenum, five days after anemia had been produced for eighty-five minutes. Slight superficial necrosis of gastric mucosa.

acutely ill for several days following trauma to the duodenum. Vomiting was sometimes observed, but there was always a marked and rapid loss of weight, so that emaciation and infections of the skin frequently followed.

The acute ulcers of the duodenum all healed rapidly, leaving scar tissue in the area of the healed lesions. Thinning of the wall and slight dilatation were frequently found in these areas. Adhesions to

the clamped areas always occurred. In animals in a poor state of nutrition, trauma to the duodenum was always followed by a more prolonged period of illness, usually from fourteen to twenty days. There was also a slight delay in the healing time of the ulcers.

GROUP 3.—In this group, the pancreatic duct of three animals was ligated with silk, and at the same time clamps were applied from thirty-three to sixty-five minutes to the duodenum and lesser curvature of the stomach near the pylorus. There was a marked disturbance of nutrition

TABLE 4 (group 3).—*Synopsis of the Protocols of Three Dogs with Ligated Pancreatic Duct and Trauma to Stomach and Duodenum Caused from Clamps*

Experiment	Date	Operation	Duration, Minutes	Return of Circulation, Seconds	Postoperative Course and Exploratory Laparotomy: Interval Days	Postoperative Course and Exploratory Laparotomy: Results and Remarks
12	12/14/26	Ligated major pancreatic duct with silk; Young's clamp applied to lesser curvature of stomach 4 cm. from pylorus and to duodenum 3 cm. from pylorus	50	15	35	Sick three weeks; emaciated and skin infections present; adhesions to clamped areas, no palpable defects in mucosa
13	2/18/27	Ligated major pancreatic duct 12/14/26; Young's clamp applied to duodenum 3 mm. from pylorus	33	Instantly	4	Vomited second day after operation, emaciated and cachetic; died fourth day after operation from peritonitis; catarrhal inflammation and petechiae gastric mucosa; acute ulcer in duodenum nearly healed 1 by 0.4 cm. near pylorus
14	12/16/26	Ligated major pancreatic duct; Young's clamp applied to pyloric end of stomach and to duodenum 2 cm. from pylorus	50	10	20 64	Emaciated; skin infections; adhesions to clamped areas of stomach and duodenum; no palpable defects in mucosa of clamped areas
15	2/18/27	Ligated major pancreatic duct; Young's clamp applied to duodenum, 1 cm. from pylorus	35	3	18 22	Vomited second day after operation; emaciated; skin infections; adhesions to clamped area of duodenum; no palpable defect in mucosa
16	1/24/27	Ligated major pancreatic duct; Young's clamp applied to duodenum, 2 cm. from pylorus	65	20	14 30	Some loss of weight; appetite poor; no vomiting; animal completely recovered; nutrition good; adhesions to clamped area of duodenum; no palpable defect in mucosa

in all the experiments of this group. When the dogs were examined from fourteen to sixty-four days after the operation, it was found that the ulcers healed rapidly, with scar formation. Subsequent applications of clamps to the duodenum of these dogs were followed by a marked loss of weight and a longer period of convalescence, usually from three to four weeks. The healing time of the ulcer was also delayed. One of the animals died of peritonitis four days after the application of a clamp to the duodenum for thirty-three minutes. There was a nearly healed superficial ulcer of the mucosa. The acute ulcers of the duodenum were typical, well defined, punched-out lesions.

Fig. 7.—Photomicrograph of margin of ulcer in figure 6. Proliferation of mucosa at margin of ulcer, necrosis of submucosa and muscularis; × 60.

Fig. 8.—Photomicrograph of scars in the mucosa of the duodenum. Note the mucosa inclusion in scar tissue of the submucosa and muscularis, beneath the healed ulcer; × 60.

GROUP 4.—Six healthy dogs were used to determine the effects of trauma from clamps on those parts of the intestinal tract not directly subjected to peptic activity. The same factors of pressure and time of application were observed. Three of the animals were killed with ether anesthesia on the next day. The remaining three dogs were subjected to exploratory laparotomy and killed after seven, fifteen and thirty-one days. Gross lesions of the jejunal mucosa did not occur after

Fig. 9 (dog 8, group 2).—Puckered scar of duodenal mucosa, forty-five days after pressure had been applied for fifty minutes is indicated by *a;* an acute ulcer of the duodenal mucosa, five days postoperatively, by *b*.

an application of rubber-covered stomach clamps for thirty minutes in a posterior gastro-jejunostomy, that is, when the clamps were applied for coaptation and not for hemostasis. An acute ulcer developed in the midportion of the jejunum of this animal when clamps were applied forty minutes for hemostasis. The ulcer was superficial and well defined, but the base contained areas of normal mucosa and was

TABLE 5 (group 4).—*Synopsis of the Protocols of Six Dogs with Trauma to the Jejunum, Ileum and Colon Caused by Clamps*

Experiment	Date	Operation	Duration, Minutes	Return of Circulation, Seconds	Postoperative Course and Exploratory Laparotomy: Interval Days	Postoperative Course and Exploratory Laparotomy: Results and Remarks
17	12/17/26	Young's clamp applied to first portion and lower jejunum	50	20	31	Very sick 10 days, marked loss of weight; omentum and loop of ileum adherent to clamped areas of jejunum; no palpable defect in mucosa; mucosa of jejunum grossly normal; strands of scar tissue and few round cells in areas traumatized shown microscopically
18	12/20/26	Young's clamp applied to first and midportion of jejunum	60	15	15	No vomiting; very sick 12 day with marked loss of weight; omentum and loop of ileum adherent to clamped areas of jejunum; no palpable defects of mucosa; jejunum resected showing puckered scars at site of clamps 1 by 0.6 cm.; strands of scar in all layers, especially the muscularis, also round cells shown microscopically
19	12/22/26	Posterior gastrojejunostomy, stomach clamps used for coaptation only; Young's clamp applied to midportion of jejunum	30 40	5 15	7	No defects in mucosa at site of gastro-enterostomy; acute ulcer 1 by 0.8 cm. and 0.1 cm. deep of second clamped area; normal mucosa in center of ulcer; necrosis present, mainly at periphery of lesion; marked proliferation of mucosa at margin shown microscopically
20	2/ 7/27	Young's clamps applied to lower jejunum and to first portion of ileum	50	10	1	Acute ulcer in clamped area of jejunal mucosa, 2.5 by 1 cm. and 0.1 cm. deep; base granular and not punched out; also two similar superficial ulcers 1.2 by 0.6 and 0.1 cm. deep in mucosa of ileum
21	2/ 8/27	Young's clamp applied to ileum, 15 cm. from ileocecal valve and to cecum	45	5	1	Colon tonically contracted 4 cm. on either side of slightly reddened and edematous clamped area; mucosa of colon grossly normal; no changes in mucosa of ileum grossly, and only slight edema of the wall, externally
22	2/ 9/27	Young's clamps applied to midportion of ileum and descending colon	50	10	1	Slight redness and edema of wall of ileum at site of clamps and two areas, 1 by 0.4 cm. and 0.1 cm. deep in the mucosa; margins sharp and smooth, base red and granular; colon tonically contracted 5 cm. on either side of slightly reddened and externally edematous clamped area; mucosa grossly normal

granular and hemorrhagic. On exploratory laparotomy after seven days, there were signs of rapid healing, and after fifteen and thirty-one days, scarcely perceptible scars of the mucosa were noted. Microscopically, scar tissue was found in all healed lesions. In the lower jejunum, the first and midportion of the ileum, superficial areas of necrosis of the mucosa were found when clamps were applied for from forty-five to fifty minutes. In the terminal 15 cm. of the ileum, an application of clamps for fifty minutes did not produce any gross evidence

Fig. 10 (experiment 9, group 2).—Sloughing of the duodenal mucosa in the clamp line of stomach clamps three days after application.

of injury to the mucosa. Necrosis of the mucosa in the colon did not occur after pressure had been used as long as fifty minutes, but the colon was tonically contracted from 4 to 5 cm. on either side of the traumatized area. This condition of extreme tonicity from mechanical irritation was not observed in any other portion of the gastro-intestinal tract. The acute ulcers occurring in the lower jejunum and ileum did not have the digested out appearance of those produced in the duodenum. The local and general reaction to trauma was less marked in the lower

intestinal tract than that observed with injury to the duodenum. Convalescence was more rapid; there was no vomiting and less loss of weight. Carlson,[30] Luckhardt [31] and others have observed a marked general reaction in dogs following manipulative trauma to the duodenum.

COMMENT

It has been shown in these experiments that injury to the mucosa of the duodenum and jejunum occurs from pressure at the line of the

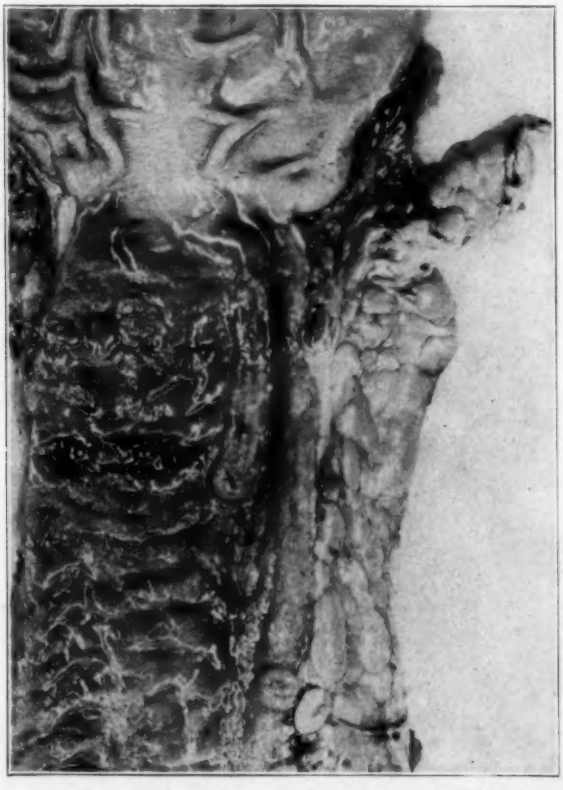

Fig. 11 (experiment 11, group 2).—An acute superficial ulcer of the duodenum after anemia had been produced for thirty-two minutes, twenty-four hours postoperatively.

clamp and that permanent scar tissue results from this injury, verifying the observations of many clinicians and of some investigators.

In group 2, typical acute ulcers occurred when the pressure was sufficient to produce blanching for over thirty minutes, while the pro-

30. Carlson, A. J.: Personal communication to the author.
31. Luckhardt, A. B.: Personal communication to the author.

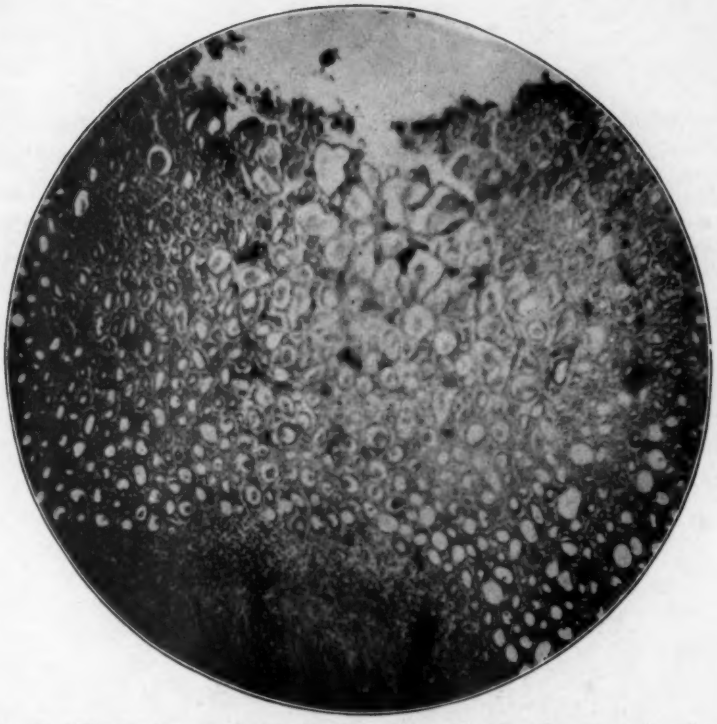

Fig. 12.—Photomicrograph of ulcer in figure 11, showing necrosis of mucosa extending to submucosa, with superficial sloughing; × 60.

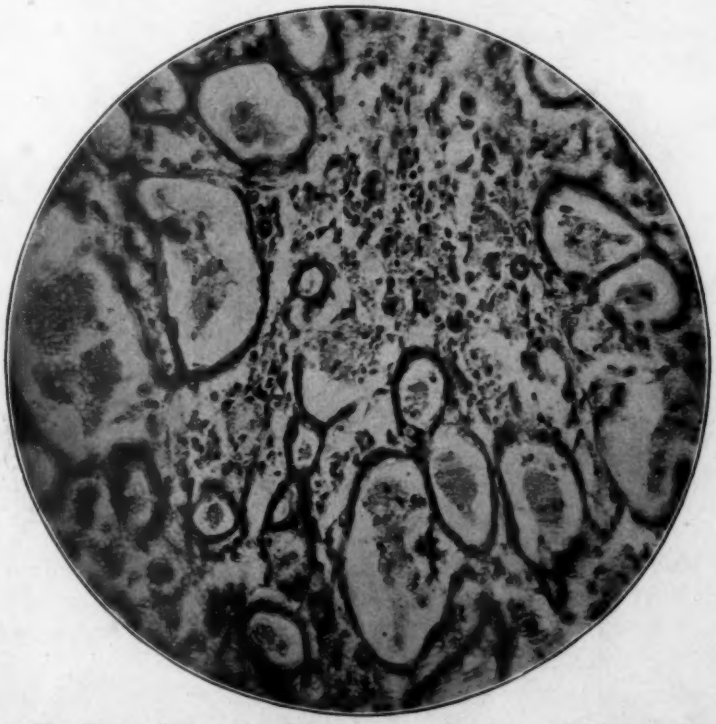

Fig. 13.—Photomicrograph of area near submucosa of ulcer in figure 11, showing exudate, dilatation of tubules of mucosa, with flattening, elongation and necrosis of the cells; × 100.

duction of a local anemia for fifteen minutes was not followed by a grossly visible lesion of the mucosa of the duodenum or jejunum. This explains, in part at least, the opinion of Kausch [9] that the apparent geographic distribution of postoperative jejunal ulcer was really a difference in the factor of trauma from clamps in the hands of various surgeons. It is a well known surgical fact that the element of time and the amount of compression are extremely variable. Experimentally

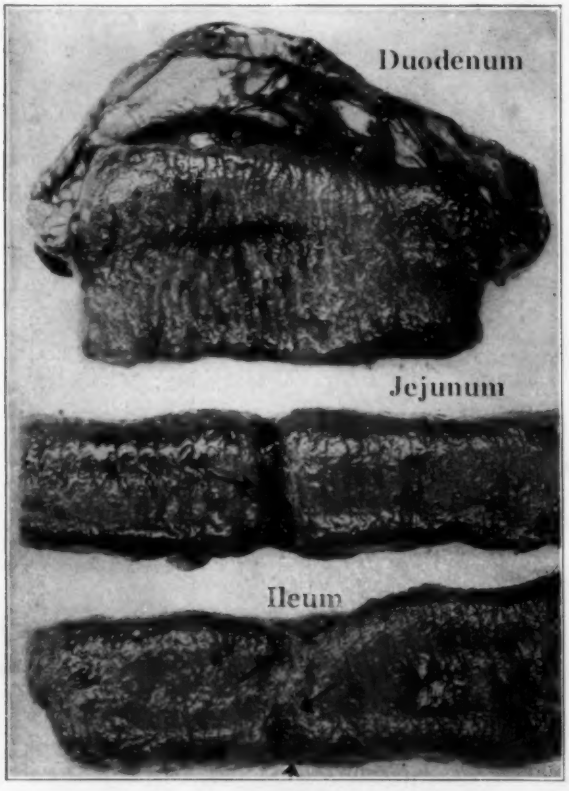

Fig. 14 (experiment 20, group 4).—Normal duodenal mucosa after 100 mm. of mercury were applied for thirty-eight minutes; superficial ulcer of the lower jejunum, anemia pressure applied for fifty minutes, and two superficial areas of necrosis of the mucosa of the first portion of the ileum, pressure applied for fifty minutes.

it was observed that these two factors were most important in the production of acute ulcers. The acute ulcers healed rapidly, confirming the observations of numerous other investigators. Scar tissue was observed in all healed lesions, and in one case, a proliferating included portion of mucous membrane was seen in the deeper areas of the scar—

a condition observed by Wilson and McCarty [32] and Spilsbury [33] in the healing of chronic peptic ulcers in man. It is reasonable to postulate that a peptic ulcer may later occur in these healed scarred areas of lowered resistance, or the acute ulcer produced by injury from clamps may become chronic when it is constantly acted on by unneutralized gastric juice. Bolton [34] believes that all chronic ulcers begin on an acute lesion.

The poor state of nutrition of the animal somewhat delayed the healing time, but in no case did the ulcer become chronic, verifying the observations of many other workers. The time of the return of the circulation to the clamped area bore an important relation to the incidence of acute ulcer in the duodenum and jejunum. When the color returned promptly after removal of the clamp, necrosis of the mucous membrane was superficial or entirely absent, grossly; while if the circulation was observed to return in from five to fifteen seconds, necrosis and sloughing of the mucous membrane were noted. The area of lowered resistance from the disturbed circulation was apparently digested out by the action of the gastric juice. This was observed particularly in the duodenum close to the pylorus.

In group 3, in which the major pancreatic duct was ligated, a marked disturbance of nutrition resulted. The removal of at least a part of the normal alkalinizing medium and the cachexia delayed the healing time of the ulcer and prolonged the period of convalescence. Ivy noted a delay in the emptying time of the stomach in which there were acute duodenal ulcers.

Chronic ulcers did not result in this group, although Jona [35] reports chronic duodenal ulcers following ligation of one pancreatic duct.

The lesions produced in the lower parts of the small intestine of group 4 were always superficial and did not have the washed-out appearance of acute ulcers in the duodenum. This is probably due to the absence of the digestive action of the gastric juice, since the same factors in the production of these lesions were observed in both instances.

The mucosa of the large bowel, as well as that of the stomach, was resistant to trauma from clamps. Acute gross injuries were not observed, although similar pressures produced acute perforating ulcers

32. Wilson, L. B., and McCarty, W. C.: The Pathological Relationship of Gastric Ulcer and Gastric Carcinoma, Am. J. Med. Sc. **138**:846, 1909.

33. Spilsbury, B. H.: Morbid Anatomy and Histology of Gastric and Duodenal Ulcer, Proc. Roy. Soc. Med. **15**:25, 1922.

34. Bolton, Chas.: Ulcer of the Stomach, Arnold, 1913, p. 396.

35. Jona, J. L.: Experimental Study of Duodenal Ulcer, M. J. Australia **1**:316 (April 19) 1919.

in the duodenum. The protective influence of a thicker musculature and a more mobile mucous membrane of the stomach and colon probably explain the absence of gross injury from clamps.

SUMMARY

The literature on the influence of trauma from clamps in postoperative jejunal and chronic experimental ulcer has been briefly reviewed.

A series of experiments on four groups has been described. In the first group a study was made of the blanching pressure in millimeters of mercury on the gastro-intestinal tract of ten dogs. It was found in these experiments that localized anemia produced for forty minutes resulted in superficial ulcers of the duodenal mucosa, while pressures less than that necessary to produce blanching for forty minutes did not result in acute ulcers. The results of these experiments were used in the application of clamps.

In the second group, ten dogs were subjected to trauma from clamps applied to the duodenum and stomach near the pylorus for from fifteen minutes to one hour and twenty-five minutes. Acute peptic ulcers were found in the duodenum when local anemia was produced for more than thirty minutes. Gross changes did not occur in the mucosa when pressure was applied for fifteen minutes; microscopically, erosions and cellular exudate were found after twenty-four hours. All of these acute ulcers tended to heal rapidly with permanent scar tissue, thinning and slight dilatation at the site of the healed lesion and with adhesions to the area externally. In the stomach, only microscopically visible changes were produced by injury from clamps; in the acute stages, superficial erosions of the mucous membrane with cellular exudate in the deeper layers and in the later stages scar tissue were present. Marked toxic reaction followed trauma to the duodenum. A poor nutritional condition of the animal resulted in a delay in the healing of the ulcer in many experiments.

A series of gastric analyses was made on three animals that had acute duodenal ulcers; a delay in the emptying time was not observed, but a slight increase in acidity was present in two dogs in which the acidity was abnormally low.

In a series of six experiments on three dogs in group 3, ligation of the pancreatic duct and trauma to the duodenum from clamps resulted in emaciation and cachexia, vomiting and a delay in the healing time of the ulcers. The scar tissue in the healed areas was not unlike that observed in group 2.

The effect of injury from clamps to the jejunum, ileum and colon was studied in six animals in group 4. Acute ulcers of the mucosa of the jejunum and first two thirds of the ileum were found. These ulcers

were superficial, healed rapidly, with the formation of scar tissue, but did not have the digested out appearance of ulcers observed in the duodenum. Grossly visible injury of the mucosa of the lower ileum and colon were not noted when clamps were applied for as long as fifty minutes. A spastic condition of the colon from 4 to 5 cm. on either side of the traumatized area was found twenty-four hours later.

CONCLUSIONS

1. Typical acute ulcers of the duodenal mucosa result from the application of clamps for thirty-two minutes when the pressure applied is sufficient to produce a local anemia; if continued for longer periods of time, greater destruction of tissue results.

2. Acute ulcers produced by clamps heal rapidly with the formation of scar tissue and a moderate dilatation and thinning of the wall of the duodenum at the site of the healed lesion.

3. Trauma of the duodenum produced by clamps in animals in a poor state of nutrition with a ligated pancreatic duct produces acute ulcers which show a slight delay in the time required for healing.

4. Trauma to the duodenum in dogs causes marked local and general reactions.

5. Acute ulcers of the jejunum and upper ileum produced by clamps are superficial, heal rapidly and do not have the digested out appearance of acute ulcers observed in the duodenum.

6. The gastric mucosa and that of the large bowel are resistant to trauma from clamps.

7. From the experiments to date, it appears clear that in dogs mechanical pressure on the duodenum and the jejunum sufficient to stop the flow of blood in the compressed part for about thirty minutes induces typical acute ulcers, which on healing leave typical scars.

8. Trauma produced by clamps may be a contributing factor in the genesis of some forms of chronic experimental ulcer in dogs.

FATE OF FOREIGN BODIES IN VENOUS CIRCULATION *

H. J. WARTHEN, JR., M.D.
RICHMOND, VA.

Several years ago, Sheppe [1] reported a case at the University of Virginia Hospital in which a bullet entered the abdomen and lodged in the wall of the inferior vena cava. During an attempt to remove it, the bullet escaped from the operator's fingers and disappeared. The rent in the vessel was closed. The patient reacted well from the operation, but died several days later from acute generalized peritonitis. Necropsy revealed the bullet firmly fixed near the apex of the right ventricle. Careful auscultation just before death failed to disclose any signs of cardiac disfunction.

During the World War many cases were reported in which foreign bodies, usually projectiles and shell fragments, entered a vein and later migrated to the heart. Tuffier [2] described a projectile, followed radiologically, which entered the right lumbar region, gradually eroded into the lumen of the inferior vena cava and six weeks later reached the right ventricle of the heart. Lyle [3] reported a case in which a shell fragment entered the femoral vein in the left thigh and migrated to the heart. The patient died four days later from general gas bacillus infection evidently due to infected fibers of clothing found with the shell fragment in the right ventricle. Mennett [4] observed a projectile roentgenologically in the right ventricle for two days. It had entered the liver and worked into the vena cava, finally reaching the right ventricle. Bailey [5] reported a most unusual case in which a toothpick was swallowed, pierced the duodenum and entered the vena cava. It was carried to the heart where it lodged in the right auricle and proved fatal by puncturing the wall of the auricle.

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* From the Department of Surgery, St. Elizabeth's Hospital.

1. Sheppe, W. M.: An Unusual Gunshot Wound of the Inferior Vena Cava, J. A. M. A. **78**:1890 (June 17) 1922.

2. Tuffier, T.: Paris letter, J. A. M. A. **70**:1181 (April 20) 1918.

3. Lyle, H. H. M.: Migration of Shell Fragment from Right Femoral Vein to Right Ventricle of Heart, J. A. M. A. **68**:559 (Feb. 17) 1917.

4. Mennett, F.: Radiologic Observation of a Projectile in the Right Ventricle Which Had Reached There Through the Inferior Vena Cava, Bull. Acad. de méd., Paris **79**:148 (Feb. 9) 1918.

5. Bailey, C. H.: Case of Foreign Body (Toothpick) in Heart, Arch. Int. Med. **11**:365 (April) 1913.

Grandgerard [6] operated on a patient with a shrapnel ball in the hypogastric vien, which the roentgen ray had originally shown to be in the right auricle. After the first radioscopic examination had showed the projectile in the auricle, a second examination after the patient was turned revealed the bullet in the femoral vein within Scarpas' triangle. A third fluoroscopic examination showed that the bullet had again changed its position and was then in the hypogastric vein. An operation was performed immediately and the vein was ligated around the bullet to prevent further wanderings. Birkbeck and Lorimer [7] reported a case in which a bullet entered the upper abdomen and migrated to the right ventricle. Gray removed it from the heart under local anesthesia. Death resulted four days later from multiple pulmonary infarction. Le Forte [8] on two occasions successfully removed projectiles from the cavities of the heart.

A review of the literature leaves one with the impression that wandering foreign bodies in the venous circulation are carried by the blood stream to the heart where they are kept in motion by the churning action of the heart, or become entangled in the chordae tendinae of the right ventricle and gradually embedded in the endocardium. No mention is made of foreign bodies reaching the lungs. Keith [9] stated, "There is no record of such a bullet being carried into the pulmonary artery; that is a remarkable circumstance."

EXPERIMENTS

In an effort to determine the course taken by foreign bodies in the venous circulation and their ultimate lodging place, objects of various sizes and shapes were inserted in the veins of a series of dogs. Dogs were chosen because of the size and accessibility of their veins, and the anatomic and physiologic similarity of their cardiovascular apparatus to that of man. The divisions of the right and left lungs into four and three lobes, respectively, and the less firmly fixed mediastinum in the dog, which makes intrathoracic surgery more difficult, are the chief points of difference between the heart and lungs of dog and man.

Prior to each experiment, morphine was administered hypodermically. The operations were done under local or ether anesthesia. The dogs were killed by over administrations of ether, by incision of the chest wall while anesthetized and by strychnine injected hypodermically.

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6. Grandgerard: Rapid Migration in the Venous Network of a Shrapnel Ball in the Right Auricle, Paris méd. **22**:48 (Jan.) 1917.

7. Birkbeck and Lorimer: Removal of Bullet from the Right Ventricle of the Heart Under Local Anesthesia, Brit. Med. J. **2**:561 (Oct. 16) 1915.

8. Le Forte: Projectiles in the Heart Cavities, Bull. Acad. de méd., Paris **80**:47 (Aug. 6) 1918.

9. Keith, A.: Loose Bullets and Foreign Bodies in the Heart, Brit. M. J. **1**:278 (Feb. 24) 1917.

The femoral and jugular veins were used, four different regions being thus afforded for the insertion of foreign bodies in each dog. Each vein was dissected out, ligated distally and clamped proximally with bulldog forceps. A nick was made in the wall of the vessel between these points. The foreign body was inserted in the vein, the bulldog forceps were removed and the object was pushed toward the heart by an injection of salt solution, or by the point of a clamp. The vein was then ligated proximal to the opening and completely divided between the ligatures. Considerable difficulty was experienced in the early operations owing to the disproportion between the size of the vein and the foreign bodies, and the tendency of the bullets to remain in the femoral vein and not to enter the general venous system. Later, this was overcome by dilating the vein just before inserting the bullets, and by using nails of smaller diameter and of greater length.

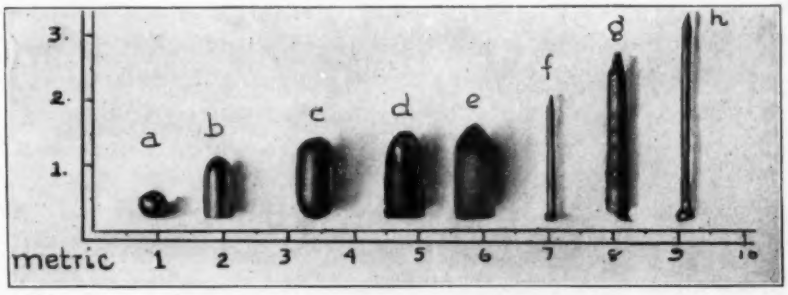

Fig. 1.—Types and sizes of bullets and nails introduced into veins; *a*, shot; *b*, bullet number 4; *c*, bullet number 1; *d*, bullet number 2; *e*, bullet number 3; *f*, *g* and *h*, nails and nail fragments.

Sterile bullets were used at first, but later unsterile foreign bodies were introduced into the circulation in an effort to determine what difference, if any, this would make in the ultimate outcome of the experiments. These unsterile objects were not grossly septic, but they had not been sterilized prior to their insertion into the vein. With this exception the experiments were done with the usual aseptic technic observed in surgical operations. Bullets and shot of four different sizes and shapes and three types of nails and nail fragments were used in order to diversify the conditions as much as possible (fig. 1).

In the earlier experiments foreign bodies of steel and lead approximating the size and shape of bullets of 5 and 6 mm. caliber and varying in length from 10 to 13 mm. were used. Later, shot about 4 mm. in diameter and nails and segments of nails varying from 18 to 32 mm. in length were used. In the first series only one foreign body was inserted in each dog at an operation, but in the later experiments several bullets

or nails were introduced at each operation. The largest number of foreign bodies were placed in dog 11 when sixteen bullets and shot were introduced during two operations.

Dog 1.—On May 10, 1926, under local anesthesia, one sterile number 1 bullet was inserted in the left femoral vein of a large adult female shepherd dog. The heart rate became slower and slightly irregular. No other immediate symptoms were noted.

On May 27, the roentgen ray showed a bullet in the lower lobe of the left lung.

On May 27, under ether anesthesia, two sterile number 2 bullets were inserted in the right femoral vein. No immediate symptoms were observed.

On July 1, the roentgen ray showed three bullets in the left lung.

On July 1, the dog died at the beginning of the operation, owing to the over-administration of ether.

Necropsy showed that the animal was well nourished. Two bullets were found in the left lower lobe, and one in the middle lobe of the left lung. The lungs did not show any macroscopic changes. The heart and abdominal viscera were negative.

Dog 2.—On May 24, 1926, under ether anesthesia, one sterile number 1 bullet was inserted in the left femoral vein of a medium sized adult female hound. No immediate symptoms were observed.

On July 6, under ether anesthesia, two sterile number 1 bullets were inserted in the right femoral vein. No immediate symptoms were observed.

On July 13, the dog was killed.

Necropsy showed the dog to be well nourished. Three bullets were found in the lungs. The lungs and heart did not show any macroscopic changes. The abdominal viscera were negative.

In the microscopic examination, the lung showed areas similar to the gray hepatization stage of pneumonia. There was a slight bronchitis. The heart showed diffuse parenchymatous degeneration, with round cell infiltration.

Dog 3.—On May 24, 1926, under ether anesthesia, one sterile number 1 bullet was inserted in the left femoral vein of a large old male shepherd dog. No immediate symptoms were observed.

On May 27, the roentgen ray showed a bullet in the left lung.

On May 27, under ether anesthesia, one sterile number 2 bullet was inserted in the right femoral vein. No immediate symptoms were observed.

On July 8, under ether anesthesia, two sterile number 3 bullets and four unsterile shot were inserted in the right jugular vein. There were no immediate symptoms.

On July 11, fluoroscopic examination showed three bullets in the left lung, and one bullet in the right lung.

On July 13, the dog was killed.

Necropsy showed the dog to be well nourished. Three bullets were found in the left lower lobe, and one in the right lower lobe. The lungs macroscopically appeared normal. The heart and abdominal viscera were negative. Four shot failed to leave the right jugular vein owing to faulty insertion.

Dog 4.—On June 23, 1926, under local anesthesia, two sterile number 3 bullets were inserted in the left femoral vein of a large adult male bulldog. No immediate symptoms were observed.

On July 1, fluoroscopic examination showed the bullets in the left lung.

On July 8, the dog died from over administration of ether prior to operation.

Necropsy showed the dog to be well nourished. The bullets were found in the middle and lower lobes of the left lung. A dry fibrinous pleurisy corresponding to the lobes containing the bullets was present on the left side. The lungs otherwise appeared normal. The heart and abdominal viscera were negative.

Dog 5.—On June 23, 1926, under local anesthesia, one sterile number 2 bullet and one sterile number 3 bullet were inserted in the right femoral vein of a medium sized adult female hound. The dog was markedly salivated immediately following the operation. This soon cleared up and no other symptoms were noted.

On July 1, fluoroscopic examination showed the bullets in the left lung.

On July 8, under ether anesthesia, one sterile number 1 bullet and seven unsterile shot were inserted in left femoral vein. It was impossible to force the foreign bodies up the femoral vein. A low midline abdominal incision was made and the bullet and shot were massaged upward. No immediate symptoms were observed.

On July 12, the dog was killed.

At necropsy three bullets were found in the left lung. The lungs did not show any gross changes. One shot was found in the apex of the right ventricle at the base of the chordae tendinae. The heart otherwise appeared normal. There were several enlarged mediastinal lymph nodes which were removed for microscopic examination. Six shot failed to leave the femoral and iliac veins owing to faulty insertion.

Microscopic examination revealed a moderate amount of fibrosis with round cell infiltration in the lungs, resembling a resolving pneumonia. There was a slight thickening of the pleura. Sections made of the heart near the site of the shot showed cloudy swelling with occasional round cells and moderate thickening of the endocardium. The lymph node was hyperplastic and contained carbon pigment.

Dog 6.—On Aug. 8, 1926, under ether anesthesia, two unsterile number 2 bullets and five shot were inserted in the right femoral vein of a large adult male hound. Three ribs were then resected and the heart was incised and sutured by the technic of Cutler and Beck. The dog died fifteen minutes later from collapse of the lungs. In dogs 6 and 7 an effort was made to keep the lungs expanded by positive pressure by means of a bellows and a tube inserted in the trachea. This proved unsatisfactory, and the lungs collapsed.

At necropsy the bullets and shot were found in the external iliac vein. The heart and lungs were normal.

Dog 7.—On Aug. 8, 1926, under ether anesthesia, one unsterile number 1 bullet and three shot were inserted in the right femoral vein of a medium sized adult female hound. A thoracostomy was done and the heart was incised and sutured as in experiment 6. The dog died twenty-five minutes later from collapse of the lungs.

At necropsy the bullets and shot were found in the external iliac vein and inferior vena cava. The heart and lungs were negative.

Dog 8.—On October 4, 1926, under ether anesthesia, two unsterile nails and four shot were inserted in the left femoral vein of a small young female hound. No immediate symptoms were observed.

On October 12, the dog had no appetite, was gradually losing weight and appeared sick.

On October 15, the dog had a slight secondary bleeding from the femoral incision.

On October 16, twelve days after operation, the dog died.

Necropsy showed the dog to be emaciated. Two shot were found in the lower lobe of the left lung. The lungs were otherwise normal. Two shot were embedded in the endocardium near the apex of the right ventricle. The heart otherwise appeared normal. The abdominal viscera were negative.

Microscopic examination of sections taken near the shot in the wall of the right ventricle showed considerable thickening of the endocardium with acute inflammation of the adjoining myocardium. The wall of the right ventricle showed cloudy swelling and occasional round cells.

Dog 9.—On Oct. 4, 1926, under ether anesthesia, one unsterile number 4 bullet, five unsterile shot and two unsterile nails were inserted in the left femoral vein of a large adult female hound. In the suturing of the incision the femoral artery was punctured and bleed freely. This was controlled by ligation of the artery. The dog reacted well immediately after the operation and apparently had no ill effects from the double ligation of the left femoral artery and vein.

On October 12, the dog did not have any appetite and was losing weight.

On October 15, the dog continued to refuse food and was rapidly becoming emaciated.

On October 17, thirteen days after operation, the dog died.

At necropsy the right pleural cavity contained several ounces of pus. An abscess about 3 cm. in diameter in the lower right middle lobe communicated with the pleural cavity. One bullet, five shot and two nails were found in the lungs. One shot was in the lower right lobe; the remaining foreign bodies were in the left lung. No bullets or shot were found in the lobe containing the abscess. The heart and abdominal viscera were negative.

Microscopic examination of sections from the lobes containing the bullets and shot showed areas resembling the gray hepatization stage of pneumonia. The margins of the abscess showed typical acute inflammation with some walling off of the abscess. Sections of the heart showed cloudy swelling but no inflammatory areas.

Dog 10.—On Oct. 19, 1926, under ether anesthesia, one unsterile number 1 bullet, three unsterile nails and one unsterile shot were inserted in the right femoral vein of a medium sized adult male bulldog. No immediate symptoms were observed.

On October 27, the dog appeared listless and had no appetite.

On October 29, the dog was becoming emaciated and used its left foreleg with difficulty. There was a swelling, apparently an abscess, near the second joint.

On October 31, twelve days after operation, the dog died.

Necropsy showed the dog to be emaciated. An abscess in the left foreleg containing about 2 ounces (0.05 cm.) of pus was opened, and two nails and one bullet were found in the wall of the abscess at a bifurcation of the brachial artery. One nail and one shot failed to leave the femoral vein owing to faulty insertion. Careful examination of the lungs and heart failed to show the point of entrance of the foreign bodies to the arterial side of the circulation. Antemortem clots, about 1 cm. in diameter, were found in both ventricles of the heart.

Microscopic examination of sections showed diffuse round cell infiltration with scattered hemorrhagic areas throughout the lungs. Definite pneumonic areas could not be made out. Sections from the heart showed slight cloudy swelling and occasional round cells, with slight thickening of the endocardium. A small ulcerated area was found in the wall of the right ventricle surrounded by an acute inflammation, with an antemortem blood clot at the margin.

Dog 11.—On Oct. 25, 1926, under ether anesthesia, one unsterile number 1 bullet and two unsterile shot were inserted in the right femoral vein of a medium sized adult female mongrel. No immediate symptoms were observed.

On November 3, under ether anesthesia, two unsterile number 2 bullets and eleven unsterile shot were inserted in the right femoral vein. No immediate symptoms were noted.

On December 20, roentgen-ray examination showed three bullets and nine shot in the left lung, and four shot in the right lung.

On December 21, the dog was killed.

Necropsy showed the dog to be well nourished. Ten bullets and shot were found in the left lower lobe, two bullets and shot in the left middle lobe, three shot in the right lower middle lobe and one shot in the right lower lobe. Macroscopic changes could not be noted in the heart or lungs. The abdominal viscera were negative.

Dog 12.—On Nov. 1, 1926, under ether anesthesia, four sterile nail fragments were inserted in right femoral vein of a medium sized adult male mongrel. No immediate symptoms were noted.

On November 8, under ether anesthesia, four sterile nail fragments were inserted in the left femoral vein. No immediate symptoms were observed.

On November 22, the dog died from an over administration of anesthetic prior to operation.

Necropsy showed the dog to be well nourished. Three nails were found in the right lung, and four nails in the lower lobe of the left lung. The lungs and heart macroscopically appeared normal. The abdominal viscera were negative. One nail failed to leave the femoral vein owning to faulty insertion.

Microscopic examination of sections of the lungs showed diffuse round cell infiltration with areas of marked congestion. There was slight pleural thickening and increased fibrous tissue throughout the lungs.

Dog 13.—On Nov. 12, 1926, under ether anesthesia, five sterile nail fragments were inserted in left femoral vein of a medium sized young female collie. No immediate symptoms were noted.

On November 21, the dog had slight secondary bleeding from the femoral incision; otherwise it appeared well.

On November 22, ten days after the operation, the dog was found dead. Death was thought to have resulted from a fight with another dog, as there had been little bleeding from the femoral incision and the dog had sufficiently recovered to permit its running at large with other dogs.

Necropsy showed the dog to be fairly well nourished, and apparently not anemic. Four nails were found in the lungs; two were together in the left lower lobe and the remaining two were in the right lung. One nail remained in the femoral vein owing to faculty insertion. The lungs appeared normal. Two small antemortem clots were found in the right ventricle of the heart. The abdominal viscera were negative.

Dog 14.—On Dec. 16, 1926, under ether anesthesia, nine sterile nails and nail fragments were inserted in the left femoral vein of a small young female airedale. No immediate symptoms were noted.

On December 20, roentgen-ray examination showed the nails in the region of the hilum of the lungs.

On December 21, the dog was killed.

Necropsy showed the dog to be well nourished. Three nails were found in the lower middle lobe and the lower lobe of the right lung. The heart was opened.

and the remaining nails were found in the pulmonary artery, with the exception of one nail fragment in the right ventricle. This had evidently fallen back into the heart owing to handling of the specimen after death, as roentgenograms made before death showed that all of the foreign bodies had passed through the heart and were in the pulmonary artery or lungs. The heart and lungs did not show any gross changes. The abdominal viscera were negative.

COMMENT

Fourteen dogs were operated on and ninety-three foreign bodies were inserted. Of these, sixteen did not reach the general venous circulation owing to faulty technic. Eleven bullets were found in the common iliac veins or in the inferior vena cava of two dogs which died in the course of secondary unrelated operations on the thorax within thirty minutes after insertion of the bullets.

Of the remaining twelve dogs only three died as a result of the foreign bodies, and these were in the second series in which unsterilized bullets and nails were inserted into the veins. Sixty-seven objects migrated to the heart, but only three were found in the heart at autopsy. The remaining sixty-four bodies were carried through the pulmonary valves into the pulmonary artery and lungs. Roentgen-ray examinations showed these foreign bodies to be in the lungs, and this was verified at necropsy. Every foreign body which reached the junction of the iliac veins was carried upward through the inferior vena cava by the current of blood. The two dogs killed soon after the insertion of the bullets demonstrated that this migration was not an immediate thing, but probably took several hours, or perhaps even days, and may not have occurred until the dogs had recovered from the effects of the operation and were again active. This increased activity probably gave the necessary stimulus to the venous circulation to carry the heavier bodies toward the heart.

In no instance were any immediate symptoms noted which could not be explained by the anesthesia used during the operation. Two dogs had slight secondary bleeding from the femoral incisions. This apparently was due to injury to the femoral artery at the time of operation.

The lung tissue in the majority of cases showed but little macroscopic change, despite the occlusion of the larger branches of the pulmonary artery by the bullets and nails. A localized dry fibrinous pleurisy was noted in one case (dog 4) in which two sterile bullets were inserted, and an abscess of the lung terminating with empyema developed following the introduction of eight unsterile nail fragments, causing death thirteen days after operation (dog 9). The results were not typical and occurred only in these two cases. It is interesting to note that the abscess of the lung developed in a lobe which did not contain any foreign bodies.

The microscopic observations were more uniform. All sections of the portions of the lungs containing foreign bodies showed pathologic changes, varying from moderate congestion with round cell infiltration to a picture simulating the gray hepatization stage of pneumonia. This probably represented the later stages of an infarct of the lung. An increase in fibrous tissue with slight thickening of the pleura was a fairly constant observation.

In the second fatal case (dog 10) two nails and one bullet passed through the heart or lungs into the arterial side of the circulation and lodged at the bifurcation of the brachial artery in the left front leg, where they caused a large abscess with death twelve days after operation.

Fig. 2.—Dog 8; heart containing two shot (indicated by arrows) in right ventricle; the dog died twelve days after insertion of four unsterile shot and two unsterile nails in the left femoral vein; two shot were found in the lungs and the remaining two near the apex of the right ventricle; the nails failed to leave the point of insertion owing to faulty insertion.

Careful gross examination of the heart and lungs failed to indicate the point where these foreign bodies gained access to the arterial side; the lungs did not show any macroscopic lesion, and the heart contained only two moderately large antemortem clots. Microscopic sections of this lung demonstrated several hemorrhagic areas and regions of moderate round cell infiltration. The wall of the heart showed slight cloudy swelling, occasional round sells and thickening of the endocardium, with a small ulcerated area in the wall of the right ventricle and localized acute inflammation and an antemortem blood clot at the margin of the ulcer.

In the third fatal case (dog 8) two shot were found to have lodged at the base of the chordae tendinae near the apex of the right ventricle, death having occurred twelve days after the operation (fig. 2). No

other cause of death could be found. Microscopic examination of the heart near the site of the bullets showed cloudy swelling and occasional round cells. There was considerable thickening of the endocardium with acute inflammation of the adjoining myocardium. The only other case in which a foreign body remained in the heart did not terminate fatally (dog 5). Ten days after the last insertion of foreign objects this dog was killed, and the shot was found at necropsy at the apex of the right ventricle (fig. 3). It had not caused any symptoms and was almost embedded in the endocardium near the base of the chordae tendinae. Three bullets of a larger caliber had also been inserted into this dog. These were found in the lungs.

Fig. 3.—Dog 5; heart containing one shot (indicated by arrow) in right ventricle; at first operation two bullets were inserted in the right femoral vein; sixteen days later one bullet and seven shot were inserted in the left femoral vein; the dog was killed five days after the second operation; at necropsy the bullets were found in the lungs; six shot remained at the point of insertion in the femoral vein; the seventh shot migrated to the heart and was found near the apex of the right ventricle.

In no instance was a foreign body found in the right auricle, or in the left side of the heart. No relationship apparently existed between the veins (jugular or femoral) in which the bodies were inserted, and their ultimate lodging place. The foreign bodies carried to the lungs by the blood stream were not symmetrically distributed throughout the lung tissue, but were most frequently found clumped together in two or three branches of the pulmonary artery (figs. 4 and 5). The majority of the objects lodged in the lower lobes of the left lung. This is probably due to a larger lumen and greater blood flow through the

branches of the pulmonary artery supplying the left lung, which in the dog has only three lobes as compared with the right lung which has four lobes.

With the exception of the two fatal cases with abscess formation there apparently was little reaction around the bullets or nails in the lungs.

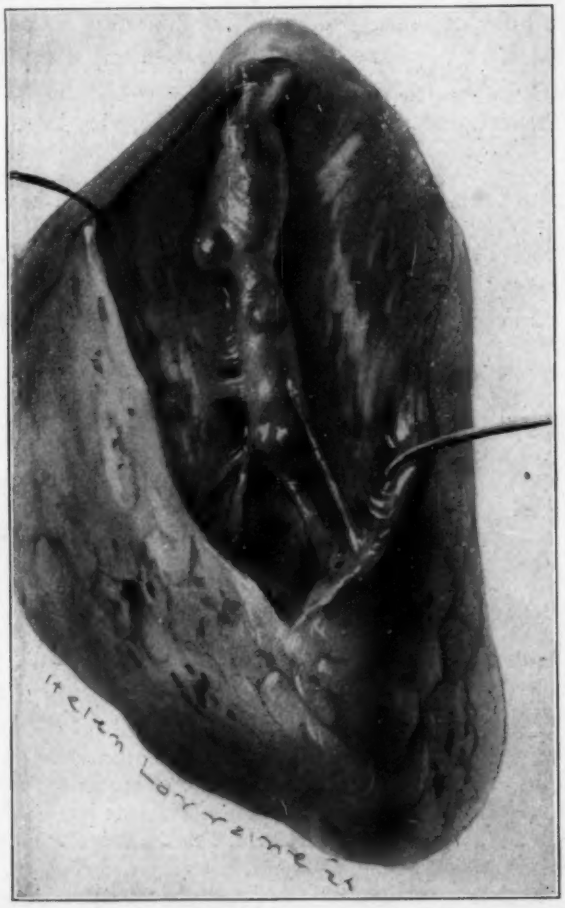

Fig. 4.—Dog 11; lower lobe of left lung showing a branch of the pulmonary artery containing four shot and two bullets; thirteen shot and three bullets were introduced into the femoral veins in the course of two operations; the dog was in excellent health when killed eighteen days after the last operation; the remaining bullets and shot were scattered throughout both lungs.

The majority of the foreign bodies were of steel, but no difference could be noted between these and those of lead. In no instance were thrombi found in the pulmonary artery, and only three small antemortem clots were noted in the right ventricle.

Fig. 5.—Dog 11; three bullets and thirteen shot scattered throughout both lungs; only four shot were found in the right lung; the remaining twelve bullets and shot were contained in the left lung.

Fig. 6.—Dog 1; one number 1 bullet in lower lobe of left lung.

Five nails in the pulmonary artery and a sixth nail which had evidently fallen back into the right ventricle, owing to handling of the specimen after death, were found in dog 14 (figs. 8 and 9). This failure to reach the lungs was probably due to the length of several of the nails, which were unable to negotiate the curve of the pulmonary artery, as three shorter nails were found in the lungs. The blood flowed around these bodies without obstruction and ill effects were not noted. One nail in this group extended halfway through a fibrous band resembling a rudimentary valve situated just above the pulmonary valves. It had doubtless passed by this valvelike septum during systole and was

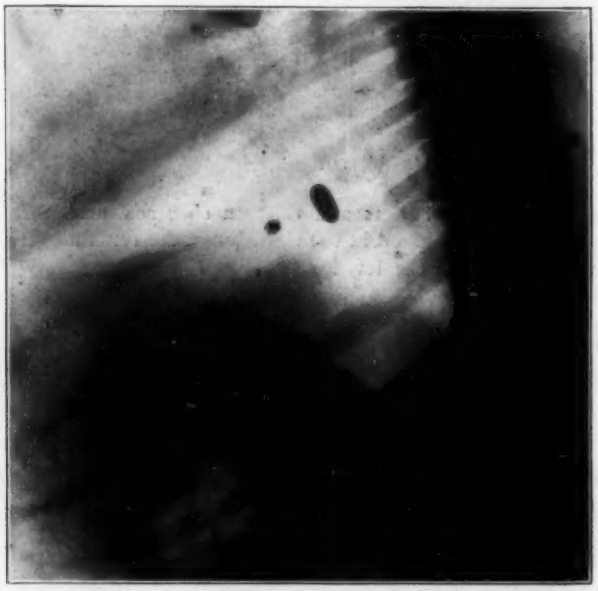

Fig. 7.—Dog 3; one number 1 bullet in lower lobe of left lung; the small shot are in the subcutaneous tissues and are evidently the result of the dog having been shot prior to the experiments.

then caught in a backflow, gradually puncturing the fibrous septum. These nails which had passed through the heart varied from 18 to 32 mm. in length. With the exception of one small antemortem clot around the nail held in the rudimentary valve, the heart and the pulmonary artery did not show any lesion resulting from the passage of these irregularly shaped objects, and the dog appeared in good health.

The recent work of Cutler [10] and his associates in surgery of the heart has opened a new field, and serves as a stimulus to further studies

10. Cutler, E. C.; Levine, S. A., and Beck, C. S.: The Surgical Treatment of Mitral Stenosis: Experimental and Clinical Studies, Arch. Surg. **9**:689 (Nov.) 1924.

in this phase of surgery. Beck [11] described a technic of suture in heart wounds which would lend itself admirably to the removal of foreign bodies within the cavities of the heart. He favors a median sternotomy or a left intercostochondral thoracotomy. The former gives a better exposure of the right ventricle. The pericardium is opened and a suture to steady the heart is placed in the apex of the heart. After the foreign body is palpated in the cavity of the heart two parallel control sutures taking a deep bite in the muscle of the heart wall are placed opposite the site of the foreign body within the heart. A longitudinal incision is

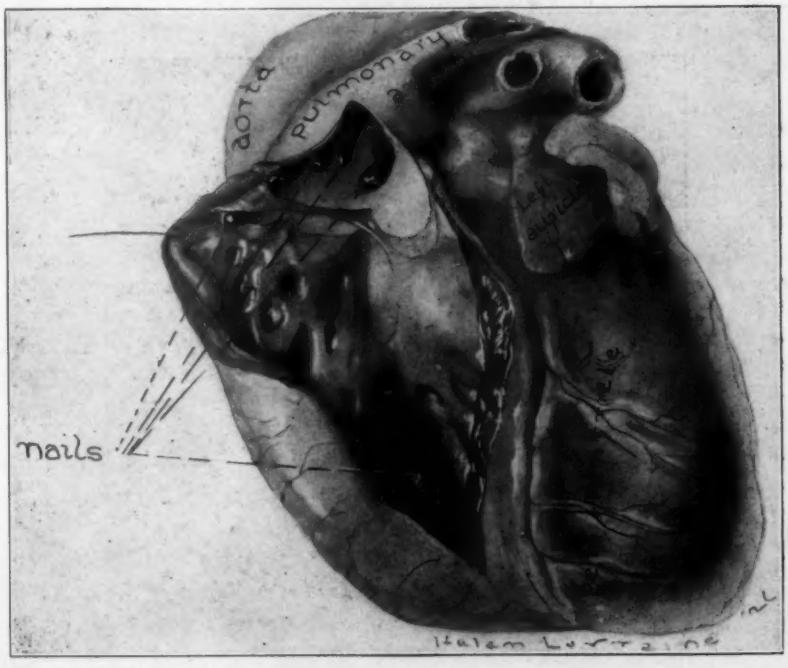

Fig. 8.—Dog-14; nails in pulmonary artery and right ventricle; dog was killed five days after insertion of nine nails in the left femoral vein; roentgenograms before death showed three nails in the right lung and the remaining six in the pulmonary artery; when the heart was opened at necropsy one nail was found in the right ventricle, evidently having fallen back due to manipulation after death; one nail is shown caught in a fibrous band simulating a rudimentary valve.

made in the tissue suspended between the control sutures, through which the foreign body is removed. The control sutures are then crossed and held under gentle traction by an assistant, thus approximating the edges of the incision while permanent sutures are placed and a neat closure is obtained.

11. Beck, C. S.: Wounds of the Heart: The Technique of Suture, Arch. Surg. **13**:205 (Aug.) 1926.

SUMMARY

The following types of foreign bodies have been discussed: Bullets inserted in venous circulation, 22; shot inserted in venous circulation, 43; nails inserted in venous circulation, 29; total number of foreign bodies, 94.

Sixteen of the foreign bodies failed to leave the femoral vein owing to faulty insertion.

Eleven were found in the external iliac vein and in the inferior vena cava of two dogs killed thirty minutes after insertion, in the course of a second unrelated operation.

Fig. 9.—Dog 14; nine nails and nail fragments; three nails were in the right lung; the remaining nails were within the pulmonary artery.

Sixty-seven foreign bodies migrated to the heart, and of this number:

Three (4.5 per cent) remained in the heart. The three animals were shot and in each the foreign body lodged near the apex of the right ventricle. Death resulted in one case.

Six (9.0 per cent) remained in the pulmonary artery, their length apparently preventing them from passing into the lungs.

Fifty-five (82 per cent) passed into branches of the pulmonary artery and lodged in the lungs. Death resulted from abscess in one dog.

Three (4.5 per cent) passed through the heart or lungs of one dog, reached the arterial circulation and lodged at the bifurcation of the brachial artery in the foreleg, causing a large abscess, and resulted in death.

The total number of dogs operated on was 14.

Two were killed immediately following operation.

Three (25 per cent) died as a result of the insertion of bullets or nails into the veins.

Twelve sterile bullets and shot were inserted in the veins of three dogs. There were no deaths.

Twenty-two sterile nails were inserted in three dogs. There were no deaths.

Forty-five unsterile bullets and shot were inserted in six dogs with death in one instance (16.6 per cent mortality). Two shot were found in the right ventricle in the fatal case.

Five unsterile nails were inserted in two dogs. Both dogs died (100 per cent mortality). One dog had an abscess of the left lung with empyema, and the other had an abscess in the left foreleg.

NOTE.—The discrepancy between the total number of foreign bodies introduced, and the number enumerated in these four groups is due to dogs 3 and 5 having both sterile and unsterile bullets and shot inserted, and dogs 9 and 10 having both bullets and nails inserted. In order to avoid this overlapping, in dogs 3 and 5 only the unsterile bullets and shot were considered, and in dogs 9 and 10 only the nails were tabulated in this summary.

CONCLUSIONS

1. Foreign metallic bodies within the lumen of a normal vein of a dog are carried by the blood stream toward the heart. This migration may take hours, or days, but eventually these wandering bodies reach the heart, irrespective of the position of the dog and the effects of gravity.

2. The majority of these objects do not remain in the heart, but are pumped into the pulmonary artery and lodge in the lungs, where they produce infarcts with apparently little disturbance to the pulmonary circulation.

3. The presence of these foreign bodies within the lungs appear to cause little discomfort. Abscess of the lung occurred only once in this series, and this abscess did not arise in a lobe containing foreign bodies. This would indicate that operative procedures in such cases would not be advisable in the absence of marked symptoms of pulmonary involvement.

4. Sterilized foreign bodies in the venous circulation do little damage to the heart or lungs, and unsterilized objects which are smooth and

symmetrical rarely cause infection. Unsterilized, irregularly shaped bodies, as nails or fragments of nails, are most dangerous and give rise to abscesses.

5. The smaller, more symmetrical and lighter objects in the venous circulation tend to remain in the heart, while the larger, more irregular and heavier bodies are carried into the lungs. Foreign bodies that remain in the heart appear to lodge near the apex of the right ventricle at the base of the chordae tendinae. This is the most accessible portion of the heart in both dog and man. The recent work of Cutler [10] and Beck [11] in intracardiac surgery provides a technic which would greatly facilitate the removal of foreign bodies from this region of the heart.

6. It is possible for objects to pass from the venous to the arterial circulation, this transition probably occurring in the lungs, without leaving any macroscopic evidence of pulmonary damage.

OPERATIONS OF NECESSITY DURING PREGNANCY*

ROBERT D. MUSSEY, M.D.
AND
JACOB F. CRANE, M.D.
Fellow in Obstetrics and Gynecology, The Mayo Foundation
ROCHESTER, MINN.

We shall discuss here conditions amenable to surgical intervention that may complicate pregnancy, but that are not the results of it. However, certain physiologic and anatomic changes incident to pregnancy may influence certain associated lesions and add to the gravity of the surgical risk. Examples of this are: (1) the rapidity with which certain types of tumors of the breast and uterus grow as a result of the increased blood supply incident to pregnancy; (2) changes in the relative position of the pelvic organs and some of the abdominal viscera caused by the enlarging uterus, with disturbance of quiescent lesions, and (3) the probability that the retardation in the filling and emptying of the gallbladder during pregnancy and the increased cholesterol content of the blood are factors in the formation of gallstones during pregnancy and even exacerbation of quiescent cholecystitis.

In the examination of women in the child-bearing age for conditions of surgical importance, one must always be alert to the possibility of pregnancy. In a review of the histories of a large group of women in the child-bearing age who presented themselves at the Mayo Clinic because of surgical lesions, it was found that approximately 2 per cent were pregnant. Certain preexisting lesions are likely to grow worse during pregnancy or, because of their situation, cause interference with the normal progress of pregnancy and labor. In determining the method of treatment to be advised in these cases, the following questions must be considered:

Is it reasonably certain that a lesion exists? Is a surgical operation the best treatment for the lesion? Will the general condition of the patient permit of operation? Does the severity of the trouble justify operation during pregnancy, and, if so, when is the best time to operate? What is the relative risk to mother and to child?

These questions must be considered from the standpoints of the type of condition and of the individual case. The surgical conditions are naturally grouped into those that may and those that may not be influ-

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* From the Section on Obstetrics, Mayo Clinic

* Read before the Pacific Northwest Medical Association, Boise, Idaho, June, 1927.

enced by pregnancy. The first group is by far the larger and the more important, as it includes intra-abdominal and pelvic lesions as well as such extra-abdominal lesions as tumor of the breast, certain types of goiter, varicose veins and hemorrhoids. The second group may be said to include surgical lesions of the head, neck, chest and extremities.

The histories of 370 women on whom it was necessary to operate during pregnancy were reviewed from Jan. 1, 1917, to Jan. 1, 1927. Before the results of this review are presented, it should be said that during this period an approximately equal number of pregnant women who presented themselves with surgical lesions did not come to operation. A third group, on whom operations were performed, is not included because subsequent data to confirm the diagnosis of pregnancy were lacking (table 1).

TABLE 1.—*Operations of Necessity During Pregnancy*

Operation	Patients	Miscarriages	Maternal Death
Appendectomy	122	2	2
Cholecystectomy with appendectomy	47	2	..
Miscellaneous on the gallbladder	27	1*	2
Partial thyroidectomy (exophthalmic goiter and edenomatous goiter with hyperthyroidism)	42†	2	..
Partial thyroidectomy (adenomatous goiter without hyperthyroidism)	13†	1	..
Myomectomy	13	3	..
On the ovary	20	3	..
On the breast	16	1	..
On the kidney	14	1	..
On the stomach	4	..	..
Miscellaneous (intra-abdominal)	14	..	..
Miscellaneous (extra-abdominal)	38	1	..
Total	370	17 (4.5 per cent)	4 (1.08 per cent)

* Miscarriage with death of mother from postoperative hemorrhage and obstructive jaundice.

† These data were collected between Jan. 1, 1916, and Jan. 1, 1926.

The list of operations performed will not be given in detail, and only the lesions most frequently encountered and those of unusual interest will be discussed. In a number of instances, more than one lesion was treated surgically at the time of operation.

COMPLICATING LESIONS

Appendicitis.—Appendicitis is a fairly common complication of pregnancy. Approximately 2 per cent of the women who presented themselves with symptoms of appendicitis were pregnant. Paddock [1] found the incidence to be 2.5 per cent. Attacks of acute appendicitis do not occur more frequently in pregnant than in nonpregnant women, but the risk of serious complications is greater in the former, and this

1. Paddock, C. E.: Pregnancy Complicated by Appendicitis, Am. J. Obst. 68:401, 1913.

risk increases progressively. The danger of operation after the fifth month is also greater. Attacks due to chronic appendicitis are more likely to recur during pregnancy, possibly because the normal regularity of the bowels is disturbed or because the cecum has been displaced by the enlarging uterus. Since the symptoms of pyelonephritis of pregnancy may simulate the symptoms of acute appendicitis, it is always necessary to rule out the former before definite diagnosis of appendicitis is made. This usually can be done by the examination of a catheterized specimen of urine from the bladder or, if necessary, from the ureter, to detect the presence or absence of pus.

Appendectomy is indicated following one or more definite attacks of appendicitis during pregnancy. One hundred and twenty-two patients were operated on for appendicitis. Two patients died, one following operation for acute appendicitis during the sixth month, and one following operation for ruptured appendix in the seventh month of pregnancy. The only miscarriages which occurred in this group were coincident with these two deaths.

Disease of the Gallbladder.—The gallbladder may become diseased during pregnancy. In 1911, W. J. Mayo [2] stated that 90 per cent of women who have gallstones and who have borne children date the onset of symptoms from a particular pregnancy.

The first symptoms may occur during the later months of pregnancy and are rarely severe enough to require surgical intervention. Frequently, however, preexisting cholecystitis will undergo exacerbation during the early months of pregnancy, and operation may be necessary. The danger of a waiting policy is much less than that in the case of appendicitis. However, when the attacks are frequent and severe or are accompanied by evidence of acute inflammation of the gallbladder, operation should be considered.

Seventy-four operations were performed on the gallbladder and ducts, and in forty-seven of these the appendix also was removed. There were two miscarriages, but no maternal deaths. In four cases, the common duct was drained at the time of cholecystectomy. One of these patients died from hemorrhage complicating obstructing jaundice, and miscarriage occurred coincident with her death. There was one maternal death following choledochotomy alone (table 2).

Pelvic Tumors.—It is often difficult to make a diagnosis of pelvic tumor complicating pregnancy or to distinguish the condition from intra-uterine or ectopic pregnancy. Even when the diagnosis of pregnancy and tumor has been made, it is not always easy to determine the type of the tumor. The differential diagnosis is important, as the treat-

2. Mayo, W. J.: Innocent Gall-Stones a Myth, J. A. M. A. **56**:1021 (April 8) 1911.

ment may vary with the nature of the tumor. In most cases of fibromyoma of the uterus, the patient will go through pregnancy and confinement without untoward symptoms. Certain fibromyomas are so situated that they will obstruct the birth canal; others may undergo degeneration, and still others may cause hemorrhage and abortion. When the tumor is situated low in the pelvis so that it is likely to cause dystocia, its removal may be necessary during pregnancy; otherwise cesarean section at term would have to be performed. Many myomas cause pain and tenderness during pregnancy; the patients are usually treated expectantly, as most of them can be carried to term. Sometimes, on account of the marked pain and tenderness and evidence of peritoneal irritation, enucleation of the myoma is found necessary during pregnancy. In the case of uterine myomas in which the patient gives

TABLE 2.—*Operations on Gallbladder and Ducts During Pregnancy*

Operation	Patients	Miscarriages	Maternal Death
Cholecystectomy	22	1*	..
Cholecystectomy and appendectomy	47	2	..
Cholecystectomy and choledochotomy	4	1†	1
Choledochotomy	1	..	1
Total	74	4 (5.4 per cent)	2 (2.7 per cent)

* Miscarriage twenty-third day after operation.
† Miscarriage; death of mother from peritonitis.

TABLE 3.—*Myomectomy During Pregnancy*

Operation	Patients	Miscarriages
Myomectomy	8	1
Myomectomy and appendectomy	4	2
Myomectomy and excision of bartholin cyst	1	..
Total	13	3 (23 per cent)

a history of previous miscarriages, apparently due to the tumor, or in which symptoms of threatened miscarriage are being produced by the tumor, myomectomy may be employed as a conservative measure. In 1920, W. J. Mayo [3] reported having performed myomectomy nineteen times during pregnancy. Five of the patients showed signs of impending miscarriage prior to operation, and in three the miscarriage was averted by the operation.

Myomectomy was performed in thirteen cases of our series. These include some cases previously reported and several others. There were three miscarriages and no maternal deaths (table 3).

3. Mayo, W. J.: Conservation of the Menstrual Function, J. A. M. A. **74:** 1685 (June 19) 1920.

Ovarian cysts are likely to cause more difficulty than myomas. Tumors of the ovary, which usually lie low in the pelvis cause dystocia, and there is danger that they may rupture during labor. It has generally been conceded that if these tumors attain considerable size they should be removed during pregnancy. The decision with regard to this must be guarded, however, and will depend mainly on the site of the tumor and on the period of gestation. In Barrett's [4] series, in which expectant treatment of the tumor was carried out, the maternal mortality was 18.4 per cent, as against 2 per cent in patients treated surgically.

Nineteen operations were performed for cystic tumors of the ovary during pregnancy. In six of these cases, salpingectomy was also performed, and in eleven cases the appendix was removed secondarily. In all but one case, oophorectomy was performed. There were three miscarriages and no maternal deaths (table 4).

It has been thought that exophthalmic goiter and adenomatous goiter with hyperthyroidism were incompatible with the continuation of

TABLE 4.—*Operations on the Ovary During Pregnancy*

Operation	Patients	Miscarriages
Oophorectomy (single)	1	..
Salpingo-oophorectomy (single)	6	2
Puncture of ovarian cyst	1	..
Oophorectomy with appendectomy	11	1
Total	19	3 (15 per cent)

pregnancy. In a review of cases of pregnancy complicating goiter published in 1926, it was found that since 1916 pregnancy had been observed in the Mayo Clinic in thirty-two patients having exophthalmic goiter and in ten having adenomatous goiter with hyperthyroidism.[5] Either ligation or partial thyroidectomy, or both, were successfully performed in thirty-four cases, and since the introduction of iodine as an aid in the treatment of exophthalmic goiter, ligations have been found unnecessary as a preliminary procedure to partial thyroidectomy. When advisable for the control of exophthalmic goiter or adenomatous goiter with hyperthyroidism, partial thyroidectomy, with proper precautions, has been performed on the pregnant woman with reasonable safety to both mother and child. Maternal death did not occur. Spontaneous abortion occurred twice and premature labor twice, apparently due largely to

4. Barrett, C. W.: Ovarian Tumors Complicating Pregnancy; Delivery, and the Puerperium, Surg. Gynec. Obst. **16**:28, 1913.

5. Mussey, R. D.; Plummer, W. A., and Boothby, W. M.: Pregnancy Complicating Exophthalmic Goiter and Adenomatous Goiter with Hyperthyoidism, J. A. M. A. **87**:1009 (Sept. 25) 1926.

other complications. In certain cases the thyroid gland enlarges during pregnancy. In most cases this is due to diffuse colloid goiter, and in some cases adenoma may be present. In fact, it is probable that a diffuse colloid goiter in a woman more than 25 years of age may contain nonpalpable adenoma. The necessity for the removal of adenomatous goiter without hyperthyroidism rarely arises during preg-

TABLE 5.—*Exophthalmic Goiter and Pregnancy* *

Treatment Prior to Use of Iodine	Cases	Miscarriages
Rest and observation	2	1
Ligation of superior thyroid artery	8	1
Ligation followed by partial thyroidectomy	4	..
Thyroidectomy (alone)	6	..
Treatment After Use of Iodine		
Iodine	5	..
Iodine followed by partial thyroidectomy	7	..

* These data were collected between Jan. 1, 1916, and Jan. 21, 1926.

TABLE 6.—*Adenomatous Goiter Complicating Pregnancy* *

Treatment in Patients with Hyperthyroidism	Cases	Miscarriages
Rest and observation	1	..
Ligation	2	..
Ligation and thyroidectomy	1	..
Thyroidectomy	4	..
Iodine thyroidectomy	1	..
Quinine and injection of urea	1	..
Treatment in Patients Without Hyperthyroidism		
Partial thyroidectomy	13	1

* These data were collected between Jan. 1, 1916, and Jan. 1, 1926.

TABLE 7.—*Operations on the Kidney and Ureter During Pregnancy*

Operation		Patients	Miscarriages
Nephrectomy	..	..	..
Tuberculosis of kidney	5	..	..
Pyelonephrosis	2	7	1
Ureteronephrectomy	..	..	..
Stone in ureter	1	..	..
Hydronephrosis infection	1	2	..
Pelviolithotomy	..	..	..
Stone in left kidney	2	2	..
Ureterolithotomy	..	..	..
Stone in right ureter	3	3	..
Total	14	14	1 (7.14 per cent)

nancy, but in some instances the size or situation of the tumor causes pressure symptoms which demand partial thyroidectomy (tables 5 and 6).

Operation is performed on the kidney during pregnancy when the lesion is such that the life or future health of the mother would be jeopardized by delay. In this series there were fourteen operations on the kidney, including nine nephrectomies. There was one miscarriage and no maternal death (table 7).

A miscellaneous group of operations was performed, including splenectomy for hemolytic jaundice in one case, resection of the stomach for carcinoma in one case, gastro-enterostomy in two cases and the closure of a gastro-enteric stoma in one case. Posterior resection of the rectum for carcinoma was performed (four and a half months' pregnancy) following a preliminary colostomy, and a living child was delivered by cesarean section at term. Five other rectal operations were performed, including hemorrhoidectomy, repair of prolapsed rectum and excision of anal fissure. There was no maternal death or miscarriage in this group. Sixteen operations were performed on the breast, including radical amputation for carcinoma in five cases, simple amputation in two cases and excision of tumor in eight cases. There was one miscarriage and no maternal death. The remaining miscellaneous operations included herniotomies, explorations, elevation of the pregnant uterus impacted in the pelvis, biopsy from the cervix for suspected carcinoma and the removal of a bleeding cervical polyp.

COMMENT

Operations of necessity were performed on somewhat less than half of the pregnant women presenting themselves with surgical lesions. The treatment of the remainder of the group depended on the nature of the lesion and on the period of gestation. Patients with gallstone colic, patients with a history of appendical attacks and patients with uterine fibromyomas should be carefully observed.

If surgical intervention is found necessary during pregnancy, it should not cause more than ordinary concern. The mortality rate is not greater than that following similar operations on nonpregnant women. The number of miscarriages is not appreciably greater as a result of the operative procedure than the normal expectancy of miscarriages during pregnancy. The time of election for operations is in the first five months, although extra-abdominal operations can be performed at almost any period of gestation. Varo [6] has emphasized the point that, if possible, pelvic operations should not be performed at a time when the menses would have occurred were the patient not pregnant. Intra-abdominal operation should not be performed after the sixth month if it can possibly be avoided.

Briefly stated, the postoperative treatment consists of the hypodermic injection of from 1/6 to 1/4 grain (0.11 to 0.16 Gm.) of morphine every four hours for the first two or three days, the amount and frequency of the dosage being gradually diminished, according to the condition of the patient. The patient is not given a laxative by mouth until the

6. Varo, B. V.: The Prevention of Abortion After Operations on Pregnancy, Zentralbl. f. Gynäk. **50**:1964, 1925.

fifth or sixth day and then only a mild one. Retention enemas of about 2 ounces (62 Gm.) of warm sweet oil may be given on the third or fourth night, to be followed the next morning by an 8 ounce (248 Gm.) simple enema. The patient is given the usual postoperative diet.

SUMMARY

Operations should be deferred until after confinement, if possible. Any necessary operation can be performed prior to the fifth month of gestation without undue risk to mother and child.

Operation for uterine myoma is rarely necessary during pregnancy. The removal of large cysts of the ovary is less dangerous to the mother than expectant treatment.

Gastrectomy, splenectomy, nephrectomy and resection of the rectum for carcinoma may be performed without undue risk during pregnancy.

TREATMENT OF INFECTION

GENERAL PRINCIPLES UNDERLYING TREATMENT FROM THE SURGICAL STANDPOINT AND THERAPEUTIC INDICATIONS TO BE DRAWN THEREFROM*

ABRAHAM O. WILENSKY, M.D.
NEW YORK

In a previous communication [1] the general mechanism of acute bacterial infection of the body was extensively discussed. Infection exhibits itself: (1) as a more or less local lesion with general manifestations derived from the absorption of toxins from bacteria, or (2) as a generally similar entity with which a bacteriemia or general blood infection is associated. In this communication I will discuss the general principles underlying the treatment of acute bacterial infection from the surgical standpoint, and will pay especial attention to the group of cases in which bacteriemia or general blood infection is demonstrable.

CLINICAL CLASSIFICATIONS

Blood cultivations of the peripheral blood can be employed in cases of acute infection for the following purposes: (*a*) in appropriate cases as an additional means of differential diagnosis; (*b*) as a means by which the severity of the infection can be gaged; (*c*) as a help in estimating the prognosis and (*d*) as criteria on which to base the primary or further operative treatment.

A relative quantitative estimation of the magnitude of the infection can be established according to the number of colonies of bacteria which appear on the plate (plate culture method) in proportion to the amount of blood used to inoculate the cuture medium in the plate; thus, one or five colonies of bacteria per cubic centimenter of blood as compared with 100 or with an uncountable number of colonies of bacteria per cubic centimeter of blood. This is a rough method and is not strictly accurate, but for practical purposes the inaccuracy is inconsequential.

Clinical Grouping According to Extent of Bacteriemia.—In practice, the presence or absence of bacteriemia or general blood infection and its relative magnitude yield the following clinical groupings, and the correct interpretation of the bacteriemia in its relation to the clinical manifestations yields certain therapeutic indications:

A. Treatment for the bacteriemia or general infection is many times not called for, as commonly the natural protective agencies of the body

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* From the Mount Sinai Hospital.

1. Wilensky, Abraham O.: The Mechanism of Bacterial Infection, Arch. Surg. **13**:228 (Aug.) 1926.

are able to destroy the bacteria and their effects as fast as the organisms and their toxins find their way into the circulation. Many times, also, as pointed out on previous occasions, the bacteriemia which accompanied the demonstrable or undemonstrable primary focus of infection at its point of entry and which was caused by it, or which in turn fathered the development of one or more demonstrable subsidiary foci of infection, was a temporary phenomenon, and sufficient time had elapsed between its appearance and the moment of observation to allow for its spontaneous disappearance. Under these circumstances, there may be no clinical or laboratory evidences of its existence. Good prognoses should be the rule under these circumstances, and the method of treatment should be planned with regard to the local focus of infection only. A reservation should be made in one's mind, however, to cover those cases of acute infection in which, for some undefinable reason as previously explained, the thrombophlebitis begins to spread; in these cases positive blood cultures may be obtained later, and the character of the illness may change entirely for the worse.

B. Blood cultures showing from one to five colonies of organisms to the cubic centimeter of blood are usually, but not always, of a mild nature, frequently show little or no evidence of their existence, are associated with symptom complexes which do not differ materially from those in similar cases in which the blood cultivations are sterile, and frequently disappear spontaneously or after operation. Good prognoses are the rule in these minor bacteriemias, and the method of treatment usually can be planned without regard to the bacteriemia.

C. On the other hand blood cultures can be obtained in which the numbers of colonies are extremely large, 100 or more colonies to the cubic centimeter of blood. This always indicates a severe infection and an extremely grave prognosis. The clinical picture commonly shows an equal evidence of the severity of the infection.

This group contains those fulminating, progressive and severe forms of bacteriema and general blood infection, the existence of which is associated clinically with a symptom complex in which a demonstrable local focus of infection is of minor and secondary consideration, and in which the bacteriemia or general blood infection is the dominating factor in the entire clinical picture. The local focus may exhibit definite signs of its presence or may be unrecognizable and undemonstrable, owing to either the paucity of its clinical manifestations or the profound intoxication produced by the general blood infection.

Any kind of local condition may be associated with such a general infection. It is to be assumed under such conditions that large numbers of viable organisms are being discharged into the blood stream from the thrombophlebitic tissue, and that the bacteria are multiplying in the

blood also; the prognosis must therefore be serious. The usual course of the condition includes a steady progression of the general blood infection until a fatality occurs.

Under these circumstances, treatment directed to the local lesion is clinically futile, and fatalities are the rule and not the exception. Even the most radical surgical procedure, such as amputation of an extremity, is of no avail clinically, and the uselessness of such a radical procedure or other procedures is usually easily recognizable by the hyperacuteness of the infection, by the extraordinary toxicity of the clinical picture and by the overwhelming rapidity with which the latter passes into one of terminal delirium, coma and death. The premise that operation on the demonstrable foci furnishes the unfortunate patient his only chance sometimes may not be refused in the presence of anxious parents and relatives; but whenever such earnest desires are acceded to, it should be unequivocably emphasized that the "chances" are practically nil. In the fulminating cases, the entire duration of the illness is often only a few days.

There are other somewhat less severe forms of acute infection in which the blood contains also large numbers of viable organisms, but in which the clinical picture does not carry with it that comparatively sudden overwhelming of the body with a profound toxemia. A somewhat more hopeful attitude can be entertained in these cases, and whenever the local conditions make it possible, the question of a radical surgical procedure should be discussed in the hope of controlling the bacteriema or general blood infection; this includes the question of amputation in infections of the bones and joints of sufficient severity in the extremities.

D. Between these two extremes are large numbers of cases in which the cultivation of the blood shows an intermediate number of colonies of bacteria. Correct judgments are more difficult in these cases. Usually an aggressive policy is indicated, and when the local foci of infection with which the bacteriemia is associated lend themselves to surgical intervention, operation should be performed with the object of removing the thrombophlebitic lesion from which the bacteriemia is derived. Thereafter watchfulness and repeated blood culture studies are necessary. A careful study of the latter permits certain deductions of therapeutic value.

In cases of this kind when a given blood culture is compared with subsequent ones taken on the same patient, decrease in the number of colonies or their disappearance undoubtedly indicates improvement when other conditions are equal; an increase in the number of colonies should always cause alarm, a prompt reconsideration of the available clinical picture and revision of all of the demonstrable foci according to rules that I shall give. Comparisons made along these lines are of extreme usefulness and importance in work at the bedside and in the operating room.

In the presence of a positive blood culture a prognosis of the ultimate outcome should not be attempted except after consideration of all the available clinical facts. While a positive blood culture is always serious, the seriousness of the possibilities is usually paralleled by the characteristics of the clinical picture. The prognosis should always be guarded. Much depends on the availability of the local focus of infection for thorough surgical removal, and on its removal before other complicating foci have appeared. Much depends also on the patient's natural recuperative powers and on the antibacterial powers of the blood serum. Instances repeatedly occur in which these powers are sufficient to overcome the demonstrable bacteriemia, so that at no time, in the absence of evidence of a fulminant and overwhelming infection as previously mentioned, should a hopeless attitude be entertained.

Infections in Which Negative Blood Cultures Are Obtained.—Negative (sterile) blood cultures obtained either primarily or secondarily should not always be associated in one's mind with the milder type of infection or with improvement. The contrary may be true and negative blood cultures may occur in the presence of the most profound infections. Negative blood cultures are obtained clinically as follows:

1. In most classes of cases, notably in furuncles, carbuncles, pulmonary and renal infections, infections in the cellular spaces or in the fascial planes, positive and negative blood cultivations of the peripheral blood are about equally common in the presence of an equally severe clinical picture.

2. In infection limited strictly to the lymphatic chains—both lymphatic vessels and lymphatic glands—positive blood cultures are not obtained. This rule seems to be absolute.

3. In streptococcus (erysipelas) cellulitis of the skin, positive blood cultures are not obtained. However, when such an infection begins in the mucous membrane of the nasopharynx and spreads outward on the skin of the face, forehead and scalp, positive blood cultures are rarely obtained.

4. In a large group of cases in which the path of infection, i.e., the path by which the bacteria communicate with the general circulation, lies through the portal area, positive blood cultures do not occur; this is especially true in pylephlebitis; and when a clinical picture is obtained sufficient to make one entertain this diagnosis, the occurrence of a positive blood culture is equally sufficient to destroy the assumption.

5. In infection of gallbladder and biliary tract, positive blood cultures do not occur either before or after operation. Positive blood cultures after operations on the gallbladder or bilary tract are usually associated with a suppurative angiocholitis and, to a less extent, with thrombophlebitic lesions which are frequently undemonstrable even at postmortem and which necessarily escape the portal area. The latter may be located in the operative wound and have no relation to the liver itself. The prognosis is extremely bad, and the patients usually go on to a fatal issue.

6. Acute infections of the pancreas—the various forms of acute pancreatitis—are not associated with positive blood cultures. These can be classified as lymphangitides of the body of the pancreas.

7. Acute splenitis—infection of the spleen (this does not include acute enlargements of the spleen associated with specific diseases such as typhoid fever, etc.)—is not associated with positive blood cultures.

8. In postpartum infection, negative blood cultures are obtained as a rule. Positive blood cultures occur as exceptions; frequently, but not always, these are found to be associated with a thrombophlebitis of the large veins derived from the uterus, which has succeeded in spreading into the internal iliac veins and into the vena cava. Radical operation is permissible only when such a pathologic condition is expected with a reasonable degree of certainty, and this measure will be successful in proportion to the ability to get beyond the thrombophlebitis when the radical hysterectomy is performed. Instances of this kind are relatively uncommon.[2]

9. In mastoid disease uncomplicated with involvement of the lateral sinus, positive blood cultures are not demonstrable. Clinically, this point has come to furnish the most important single evidence for exclusion of involvement of the lateral sinus.

10. In thrombophlebitis of the cranial sinuses, other than the lateral or petrosal sinuses, sterile blood cultures are constantly obtained. Cavernous sinus thrombosis is the best example. In the presence of a primary lesion, to which the cranial (cavernous) sinus thrombosis is secondary, a positive blood culture is sometimes obtained when the primary lesion—for example, a furuncle of the nose or face—is capable of discharging living bacteria into a blood stream.

11. In empyema thoracis strictly limited within the pleural sac and without an open communication with the pulmonary parenchyma, negative blood cultures are the rule. The occurrence of a positive blood culture should be considered an indication that some complication exists from which the positive blood culture is derived.

12. In acute peritonitis, sterile blood cultures are obtained as a rule. In the variety in which there is a distinct metastatic lesion, i.e., that secondary to an acute streptococcus tonsillitis or that secondary to a lobar pneumonia, the occurrence of a positive blood culture should be referred to the primary lesion. In the variety due to the close relationship with a primary intra-abdominal lesion, i.e., that accompanying an acute appendicitis, etc., the occurrence of a positive blood culture should be referred to some other complicating lesion; these cases are rare.

13. In acute meningitis of the suppurative variety, sterile and positive blood cultures occur about equally often. The organisms demonstrable in the blood should be referred to a thrombophlebitic lesion in close relationship with the meninges and from which the meningitis is derived.

These clinical classifications can be further combined into the following broad groups without consideration of the location of the focus of infection.

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2. The usual rule in conservative circles is not to operate in cases of postpartum infection, as it is found clinically that in large series of cases this policy results in a larger proportion of cures. I approve of this rule; but, nevertheless, I believe that it should not be allowed to stand in the way of operation when a case occurs in which the laboratory and clinical facts approach those outlined in the text.

A. The question of a positive blood culture, being intimately associated with the presence of a thrombophlebitis in which the thrombus harbors organisms actively growing on a surface in open communication with the freely circulating blood, it follows that sterile blood cultures of the peripheral blood will be obtained under the following conditions:

(*a*) When the primary focus of infection at the portal of entry on a surface of the body (skin or mucous membrane) does not contain a thrombophlebitis. In these instances the focus of infections is limited to cellular tissue or spaces in contact with lymphatic spaces or vessels. This suggests the reason why certain primary foci of infection (furuncles, carbuncles, etc.) are equally commonly accompanied by positive and by negative cultivations. In these cases the bacteria in the primary lesion may be limited and may not always be permitted to extend into a nearby vessel because of various reasons—mechanical and anatomic, antibody activity, etc.; of course, when bacteria do not enter the circulation, bacteriemia does not occur. On the other hand, if these natural barriers do not exist, or are insufficient, bacteria enter the blood stream, and bacteriemia results. For instance, this explains the difference in clinical virulence of infections of the face, the different conceptions held in different clinics regarding association with positive blood cultures, the different opinions regarding the seriousness of these infections of the face, and the different points of view regarding the correct method of treatment, i.e., conservative treatment or incision.

(*b*) The thrombophlebitis in the primary lesions does not contain living, growing bacteria.

B. Sterile blood cultures are associated with conditions in which the path of entry of the infection lies through the lymphatics.

C. Sterile blood cultures are obtained when the portal area is interposed between the point of entry of the infection and the general circulation. This seems to be associated with an antibacterial property of the liver. This fact was first established experimentally by Wyssokowitsch in 1886, and has been corroborated by others since then.

D. Sterile blood cultures may be associated with intervals between temporary states of bacteriemia. The development of secondary foci in the presence of negative blood cultures is the most powerful proof of these temporary bacteriemias. The temporary bacteriemias find their mechanisms in the repeated discharge of numbers of bacteria into the blood stream, each discharge being separated by an interval sufficiently long to allow the destruction of the organisms. Clinically, the discharge of bacteria into the circulation is often accompanied by a chill. There is abundant experimental proof (Wyssokowitsch and others) to show that the injection of living organisms into the circulation of the blood is followed by a progressive disappearance of the latter, so that while blood cultivations taken for the first hour or so after injection are positive, those taken later are negative. In clinical practice it is a common occurrence for the temporary bacteriemias to be unintentionally produced by operation and other manipulations, as for example, in the

dressing of a wound, notably a wound of the bone, the passage of a sound into the bladder and other procedures. The lesson to be learned is that manipulations of the kind which are known to cause these bacteriemias should be practiced with great care and circumspection, and should be avoided altogether if possible. Unnecessary and unwise squeezing and other treatment of lesions, notably of furuncles and carbuncles, especially of the face and upper lip, may convert a seemingly innocuous lesion into a fatal one complicated by a thrombophlebitis of the facial vein and of the cavernous sinus.

In the presence of positive and negative blood cultures, a progressive impoverishment of the general condition of the patient is frequently due to the magnitude and number of the various points of fixation that have occurred or to their location in important viscera or localities of the body rather than to the presence of the blood infection. Positive blood cultures are sometimes obtainable only at a late stage of the illness. Death results from either a general progression of the entire infection or from the results of any one particular manifestation, for instance, from the results of a localization in the lungs and pleura.

Character of Organisms Found on Culture.—Facts obtained by studying cultures of purulent or other material (exudate) obtained from a demonstrable local focus of infection also frequently serve valuable purposes. The information can be classified as follows:

A. The mere presence of organisms in the exudate serves as a means of diagnosis. The best example of this is the finding of pyogenic or other organisms in the spinal fluid.

B. The character of the infecting organism frequently serves as a means of differential diagnosis and at the same time helps materially in establishing the prognosis, i. e., the demonstration of anthrax bacilli in an otherwise indifferent looking lesion changes the outlook to an extremely grave one. In other instances the character of the organism becomes important when the lesion is in a given tissue, i. e., the presence of Welch bacilli in a focus of infection in muscle tissue makes an otherwise favorable prognosis potentially fatal. Cases are constantly being seen in which it is difficult to decide whether a focus of infection has localized in a bone or in an adjacent joint. True enough, this sometimes indicates a simultaneous involvement of both, but in other cases the localization is hidden in a general inflammatory reaction. Under these circumstances, the demonstration of organisms of the staphylococcus group—*Staphylococcus aureus* especially—indicates that the chances are greatly in favor of an involvement of the bone; the demonstration of organisms of the streptococcus group would speak in favor of an involvement of the joint. The differentiation carries with it a possible therapeutic indication. Other things being equal, the demonstration of organisms of the staphylococcus group with

its consequent interpretation of a lesion of the bone would ordinarily favor exploration of the bone in cases of doubt; while the demonstration of organisms of the streptococcus group would indicate a more conservative treatment, at least as far as exploration of the bone was concerned.

C. Recently abdominal puncture has been practiced in cases of general peritonitis, either as a method of diagnosis in doubtful cases or as a means of differentiating a pneumococcus or streptococcus peritonitis. When these organisms are demonstrable, it indicates that the peritonitis is a metastatic one and is unassociated with a definite focus of infection in an intra-abdominal viscus which is amenable to surgical treatment; the prognosis then becomes extremely grave; in Mount Sinai Hospital the usual custom is to refuse to operate in these cases.

D. In infections of the middle ear the demonstration of a mucoid encapsulated coccus is commonly accompanied by a rapid destruction of tissue, which is unaccompanied by perceptible clinical or other evidence. Exploration of the mastoid is then indicated, although with other types of bacteria operation would not be considered.

PORTAL OF ENTRY OF INFECTION

In any given case, a demonstrable bacteriemia may be referable to the original primary lesion at the portal of entry of the infection or to any secondary or subsidiary form of infection. Because of the thrombophlebitis which is produced at the point of fixation, secondary foci can also give rise to a bacteriemia; these include especially foci of osteomyelitis and a bacterial endocarditis.

Primary bacteriemias are more commonly demonstrable and recognizable as such in cases of infection by specific organisms, as, for example, the gonococcus bacteriemia accompanying an acute gonococcus urethritis or the pneumococcus bacteriemia accompanying a pneumococcus pneumonia of the lobar type Somewhat less commonly the primary bacteriemia is recognizable as being due to the original primary lesion because the latter is available for discovery and observation on an exposed surface of the body, as for example, the bacteriemia which accompanies a carbuncle or furuncle of the skin or that which accompanies streptococcus tonsillitis. Sometimes both of these factors, the specificity of the organism and the location of the lesion on a surface of the body, favor the recognition of the primary bacteriemia as such, as, for example, the bacteriemia which accompanies an anthrax lesion of the face or the bacteriemia which accompanies typhoid fever, in which the portal of entry is on the mucous surface of the ileum and the primary lesion is in Peyer's patches. Except under these specific conditions, the available instances in which the demonstrable bacteriemia

can be recognized as primary and as being derived from the primary lesion at the portal of entry seem to be in the minority.

In other cases distinct primary and subsidiary lesions coexist and are associated with a demonstrable bacteriemia. Then it is commonly difficult to say whether the demonstrable bacteriemia is derived from the primary or from the secondary lesion. The best examples of this difficulty are found in conditions of the ear in which a primary lesion is found in a complicating thrombosis of the lateral sinus, and secondary lesions are found in a bone or in a joint. Here the primary lesion remains a constant factor even in the presence of subsidiary foci which can themselves originate bacteriemias. Even after the jugular vein has been efficiently tied, a bacteriemia may still be derived from extension of the primary thrombus along the petrosal sinuses, and it is a nice distinction to integrate a bacteriemia properly between a subsidiary focus elsewhere in the body and the primary lesion in the lateral and petrosal sinuses. Some facts pertinent to this distinction will presently be referred to in discussing the situations which may arise in acute osteomyelitis.

Lastly, in still other cases a focus of infection is present which is distinctly a metastatic lesion, and which is accompanied by a bacteriemia. In the one group of such cases a primary lesion is sometimes demonstrable as a definitely healed lesion. A common example of this clinical fact is found in cases of acute hematogenous renal infections (hematogenous multiple renal infarcts); frequently, indeed, the site of the original furuncle is still recognizable in a recently healed scar. In the second and much more common group of these cases, the primary lesion is undemonstrable. The commonest example of this status is found in cases of acute osteomyelitis. In the presence of any of these combinations experience leads one to assume that for clinical purposes all of these bacteriemias should be associated with the demonstrable metastatic lesion. Fairly complicated situations can and do arise, and the lines of thought which one follows are best illustrated in the cases of acute osteomyelitis:

In many of the cases only a single focus of osteomyelitis is demonstrable. In most of the cases in this group, a comparatively small number of bacteria are demonstrable in the circulation of the blood (plate culture method). Should the bacteriemia disappear before operation spontaneously and fairly promptly, one may assume that the bacteriemia was caused by the undiscoverable primary lesion to which the demonstrable focus of osteomyelitis was subsidiary.

If the bacteriemia persists, and if it disappears promptly after an efficient operation in which the entire focus of infection in the bone is removed, the assumption seems justified that the demonstrable bacteriemia was derived from the thrombophlebitic lesion in the focus

of infection in the bone. This is the criterion which prompts active radical operative treatment in cases of osteomyelitis associated with bacteriemia.

In some of the cases, however, bacteriemia persists after operation. When the surgeon is certain that the lesion of the bone has been so thoroughly removed that it cannot cause bacteriemia, and when the appearances of the wound in the bone corroborates this impression, the bacteriemia should be considered as an indication that some other focus exists which must be found and removed in order to render the blood sterile. Many times this proves to be the case; but when it does not, the original focus of osteomyelitis should be examined again and revised operatively.

If bacteriemia persists, and if the number of demonstrable bacteria still is comparatively small, other foci or lesions capable of causing bacteriemia should be looked for. In the absence of any such demonstrable lesion, the explanation of the bacteriemia cannot be decisive, although it must necessarily be assumed under the circumstances that the original focus continues to discharge bacteria into the blood stream.

In the meanwhile, other foci should be looked for, especially during the continuation of the bacteriemia, which may subsequently be found to be due to some complicating factor unrelated to the focus of infection in the bone (intercurrent disease or some other condition). When the bacteriemia cannot be adequately explained and when it continues to exist, a bacterial endocarditis should be looked for. The presence of this condition is the most serious complication possible, and the prognosis is grave; operation on any local focus is futile in the presence of a bacterial endocarditis, and a fatal outcome should be expected.

The explanation of the bacteriemia becomes a matter of exclusion when several foci of infection coexist. Rules similar to those outlined in the foregoing paragraph apply.

TREATMENT FOR THE LOCAL LESION

Treatment for the local lesion should be based on (1) a consideration of the mechanism by which the focus is produced; (2) the character of the lesion which is produced as determined by all available knowledge, and (3) the magnitude of the infection in association with the absence or presence of bacteriemia. Multiple foci should be treated individually along similar lines and in accordance with the points of view expressed.

A. Other things being equal, the absence of a demonstrable bacteriemia or general blood infection indicates that a conservative attitude can be assumed in deciding the correct method of surgical treatment of the local focus. The immediate important results of this conservative attitude include: (1) the performance of a much less severe—frequently a minor—primary operation; (2) much less chance of the spreading of

the thrombophlebitic or thrombo-arteritic process with all the consequences outlined; (3) frequent conservation of important organs or tissues, and (4) frequent avoidance of unnecessary complications.

B. Other things being equal, the presence of a demonstrable bacteriemia or general blood infection indicates a dangerous and possibly progressive lesion; it also indicates that an urgent effort, commensurate with the severity of the infection, should be made to remove the local focus as early and as completely as possible before the spreading infection does irreparable damage to the endocardium or to some important organ or locality. All of the information classified in the previous part of this and in other papers as regards the clinical and therapeutic significance of a bacteriemia or general blood infection should be considered at this time and judgments formed and indications met accordingly.

The important indication is to remove the local focus of infection as completely as possible. Frequently, conservative treatment should be replaced by radical removal of tissue into healthy areas in an attempt to reach a point distal to the thrombophlebitic lesion. The difficulty at these early stages is the impossibility of recognizing the limits of the lesion, and much wider excisions of tissue must therefore necessarily be done than would otherwise be necessary. There are times and localities in which radical removal of the thrombophlebitic focus is not technically feasible; under these circumstances, as much as possible should be done in this direction; ample drainage should be secured as the next best treatment. A good deal must be entrusted to nature's efforts to dissipate the bacteriemia spontaneously.

Local anesthesia should never be employed in operating on foci of infection in the skin. The method lends itself to the spreading of the lesion and is equally at fault with rough manipulations or squeezing of the tissues near the infected areas. In operating on foci of infection in deep organs or tissues, local anesthesia may of course be used for the outer wound.

The phenomena associated with and accompanying a bacteriemia sometimes occur after operation—so-called "operating room infection"—in divers parts of the body. The accident is undoubtedly associated with the vascular thromboses which are a necessary incident in the healing of all operatively produced wounds. The infection of the latter does not always predicate an introduction of organisms from without, but the bacteria may come from unrecognized foci of infection preexisting in the body, as, for instance, in the tonsils; the wound then becomes a secondary focus. This is the most important reason for adequate physical examination of all patients before operation, and search should be especially directed toward otherwise obscure areas of the body.

As a general rule, postoperative infections, with demonstrable bacteriemia, are extremely serious and usually terminate fatally. Clinically, the patient has high fever and chills; the chills usually occur at irregular intervals whenever swarms of bacteria are being sent into the circulation. The local area of the operative wound need not necessarily show more evidences of change than are seen under more happy circumstances, and it is always impossible to discover any other focus of infection which could account for the bacteriemia.

In certain areas of the body and after certain operations, for instance in the pelvis, and after amputations of the breast for carcinoma, the proximity of large veins to the operative field should make one suspect that the circumstances outlined in the foregoing paragraph are associated with an infected thrombosis of the adjacent vascular channels. Exploration of these venous channels is urgently indicated; when the thrombi are found, these should be removed and the veins tied on their distal side. The latter operation will succeed in direct proportion to the shortness of time during which the thrombi has been allowed to feed bacteria into the blood stream; success will not always follow when secondary foci have been established, and never when the endocardium becomes secondarily involved.

The phenomena accompanying the spread of the thrombophlebitis are apt to occur after operation, particularly in tissues provided with an abundant vascular plexus, for example, in bone tissue. Clinically, these are recognizable by the continuation of the subjective and objective phenomena or by recrudescences or exacerbations of the process. Much more serious effects can occur in infections of the skin—furuncles, carbuncles, etc.—after operation, and the danger of spreading an old thrombophlebitis or causing a new one is directly proportionate to the proximity of the local focus of infection to an adjacent vein. I have referred to this previously in discussing local infections of the face and upper lip. For this reason, conservatism is indicated in treatment for local infections of this kind.

CHANGES IN THE CHEMISTRY OF THE CONTENTS OF THE STOMACH FOLLOWING GASTRIC OPERATIONS *

M. E. STEINBERG, M.D.

J. C. BROUGHER, M.S.

AND

I. J. VIDGOFF, M.D.

PORTLAND, ORE.

Surgeons advocating radical operation (Lewisohn [1] and de Takata [2]) and even those advocating conservative methods (Portis and Portis [3]) in the treatment of gastric and duodenal ulcers agree that gastrectomy produces a lower acidity or an anacidity in the contents of the stomach. The mechanism concerned in bringing about this change, however, is a subject of controversy. Deaver and Reimann [4] stated that the resection of the antrum does away with the area of the stomach mucosa that secretes acid. This is contrary to anatomic and physiologic facts. The antrum is lined by pyloric glands which contain no, or only a few, acid cells (Steinberg [5]). These glands secrete only an alkaline form of mucus (Babkin [6]). The relation of the mucosa of the antrum to the secretion of gastric juice was first called to our attention by Edkins. [7] This investigator found that extracts of the mucosa of the antrum mixed with other substances, such as peptone and water, and then injected into the blood stream produced the secretion of gastric juice. Edkins [7] was of the opinion that this action of the mucosa of the antrum was specific. Later, Keeton and Koch [8] found that extracts of other glands injected

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* From the Physiology Department of the University of Oregon Medical School.

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2. De Takata, G.: The Perverted Physiology of the Stomach after Gastric Operations, Am. J. M. Sc. **172**:45, 1926.

3. Portis, B., and Portis, S.: Effects of Subtotal Gastrectomy on Secretion, J. A. M. A. **86**:836 (March 20) 1926.

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5. Steinberg, M. E.: Stomach Mucosa in Ulcer and in Carcinoma, Arch. Surg. **14**:991 (May) 1927.

6. Babkin, B. P.: Die äussere Sekretion der Verdauungsdrüsen, Berlin, Julius Springer, 1914, pp. 118, 119.

7. Edkins, J. S.: The Chemical Mechanism of Gastric Secretion, J. Physiol. **34**:133, 1906.

8. Keeton, R. W., and Koch, F. C.: The Distribution of Gastrin in the Body, Am. J. Physiol. **37**:481, 1915.

into the blood stream also caused the secretion of gastric juice. Tomaschewsky [9] found that gastrin was distributed uniformly throughout the mucosa of the stomach. The work of Edkins,[7] however, stimulated an interest in the rôle that the mucosa of the antrum may play in the complicated mechanism of gastric secretion.

According to Pawlow [10] and his school, there are two main phases of gastric secretion. The first is the psychic phase, which is responsible for a great deal of the secretion of gastric juice, and which is brought about by the animal seeing, smelling, tasting and chewing food. The chemical phase is characterized by a long latent period. It is believed that the secretion from the glands of the fundus is brought about through the stimulation of the mucosa of the antrum. The flow of gastric juice can also be inhibited by the various foodstuffs coming in contact with the duodenal mucosa. In the experiments dealing with the mechanism of secretion concerned in the chemical phase, Krshyschkowsky [11] and Gross [12] have divided the dog's stomach into the pars pylorica and the fundus. In other experiments, Gross [12] has separated the duodenum from the antrum so as to study the effect of substances on the gastric secretion when they are introduced directly into the duodenum. The dogs were kept alive by an external gastro-enterostomy (fig. 4).

It was found that neutral fat, oleic acid, soaps, soda and physiologic sodium chloride solution, when introduced into the duodenum, appear to have an inhibitory influence on the secretion from the mucosa of the fundus. On the other hand, meat extracts, water, salt solution, pancreatic juice, bile, oleic acid and lactic acid, also soaps, dextrin and dextrose solution, when introduced into the antrum, stimulate the secretion of the glands of the fundus. Krshyschkowsky,[11] Zeljony [13] and Gross [12] have introduced meat, bread, milk, water, lactic acid, bile, Liebigs' beef extract and peptone into the fundal part of a dog's stomach. These substances remained in the fundus for two hours and longer without producing any secretion of gastric juice.

Babkin [6] concluded that the chemical irritation of the surface of the mucosa of the fundus of the stomach does not bring forth the secretion from its glands.

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9. Tomaschewsky, Z.: Ueber die chemischen Erreger der Magendrüsen, Arch. f. d. ges. Physiol. **170**:260, 1918.

10. Pawlow, I. P.: The Work of the Digestive Glands, London, Charles Griffith & Company, 1910.

11. Krshyschkowsky, quoted by Babkin, B. P.: Die aüssere Sekretion der Verdauungsdrüsen, Berlin, Julius Springer, 1914, p. 126.

12. Gross, W.: Beitrag zur Kenntis der Sekretionsbedinungen des Magens nach Varsuchen am Hund, Arch. f. Verdauungskr. **12**:507, 1906.

13. Zeljony, quoted by Babkin, B. P.: Die aüssere Sekretion der Verdauungsdrüsen, Berlin, Julius Springer, 1914.

Ivy [14] has emphasized that there is an intestinal phase of gastric secretion. He separated the stomach from the esophagus and duodenum. One end of the stomach was closed and the other end was brought outside by a fistula. The dog was fed in the normal manner and the food was passing from the mouth to the esophagus which was anastomosed to the duodenum. From two to four hours after the dog was fed, the isolated stomach secreted copiously. Ivy [14] has also demonstrated the humoral mechanism in gastric secretion. He was able to isolate the pouch of the stomach and separated it from the nerve and blood supply of the main part of the stomach. He transplanted this pouch under the mammary gland of a dog and found that when the dog was fed the transplanted pouch secreted gastric juice.

Since the European surgeons have begun to treat gastric and duodenal ulcers by resection of the stomach and have noted the striking change in the chemistry of the contents of the stomach, they were stimulated to theorize as to the cause of the reduction in the acidity. Lorenz and Schur [15] have reviewed a series of their material following gastrectomy. They have noticed that the size of the antrum removed was directly proportional to the reduction in the acidity. They laid emphasis on the fact that the removal of the antrum does away with the part of the stomach which is indirectly responsible for the chemical phase of gastric secretion. These authors did not believe that the neutralization of the stomach contents by regurgitation of the alkaline juices from the intestine could play any part in producing the striking change. Later, some experimental work was undertaken by Smidt,[16] who utilized the methods of the Pawlow school. He formed a Pawlow pouch and then resected the antrum and studied the change produced. He came to the conclusion that the removal of the antrum, especially after the method of Billroth I, reduces the secretion of gastric juice to a minimum. Two years later in an experimental study, Portis and Portis,[3] using the same methods as Smidt,[16] demonstrated that after gastrectomy the Pawlow pouch secretes a gastric juice high in acidity. They were of the opinion that the neutralization of the contents of the stomach by regurgitation of the intestinal juices is the most important factor in changing the acidity of the contents of the stomach after resection of the antrum.

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14. Ivy, A. C.: Contribution to the Physiology of the Stomach, J. A. M. A. **85**:877 (Sept. 19) 1925.

15. Lorenz, H., and Schur, H.: Unsere Erfahrugen über den Wert der Antrumresektion bei der Behandlung des Ulkus Pepticum, Arch. f. klin. chir. **119**:239, 1922.

16. Smidt, H.: Experimentelle Studien am nach Pawlow isolierten kleinen Magen über die sekretorische Arbeit der Magendrüsen nach Resektionen Billroth I und II, sowie nach der Pylorusausschaltung nach V. Eiselsberg **135**:26, 1923.

It is evident that investigators using the same methods have disagreed as to the real mechanism concerned in bringing about the change in the chemistry of the gastric contents after resection of the antrum. Smidt,[16] using the same methods as Portis and Portis,[8] came to the conclusion that resection of the antrum reduces the secretion of gastric juice, while Portis and Portis [8] believed that the neutralization of the contents of the stomach is the biggest factor in bringing about the change in the acidity. It remained for us to find other methods of experimentation in addition to the methods already in use in order to throw more light on the following problem: Does the removal of the antrum do away indirectly with the secretion of gastric juice in the manner of eliminating the chemical phase, or does a gastro-intestinal anastomosis after the resection bring about a change in the emptying time of the

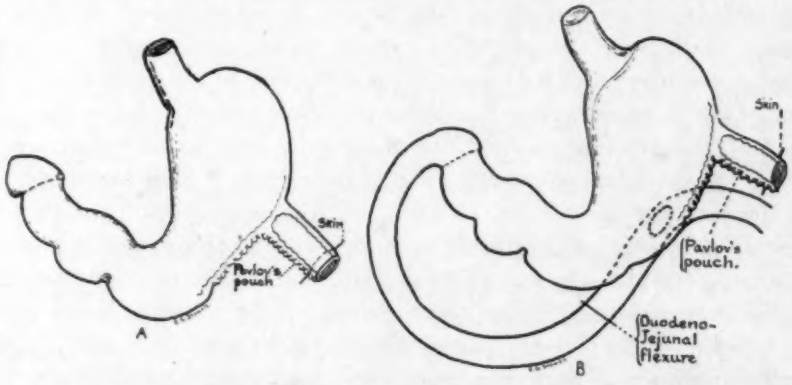

Fig. 1.—*A*, normal stomach with Pawlow pouch; *B*, normal stomach with Pawlow pouch and a posterior gastro-enterostomy.

stomach and in the regurgitation of the alkaline intestinal contents to such a degree that the changed chemistry is due to neutralization?

EXPERIMENTAL METHODS

In the course of our experiments, we have also studied the changes that are induced in the chemistry of the contents of the stomach by gastro-enterostomy alone. This part of our study, however, was incidental, since in our plan of work we have performed a gastro-enterostomy before removing the antrum. We shall discuss briefly the phase of gastro-enterostomy only, as it is related to our chief problem, since one of us (Burget and Steinberg [17]) has already published an experimental study dealing with the regurgitation of intestinal contents after gastro-enterostomy.

17. Burget, G. E., and Steinberg, M. E.: Studies on the Physiology of Gastro-Enterostomy, Am. J. Physiol. **60**:308, 1922.

In the first series of experiments, we studied the change in the quantity and the chemistry of secretion as it is affected by a gastro-enterostomy.

For this purpose, we made a Pawlow pouch from the fundus of the stomach in the manner described by Pawlow (fig. 1). We fed the dog 200 Gm. of cooked meat and noticed the normal response of the glands from the pouch (table 1 *A*). Later, we performed a gastro-enterostomy on the same animal (fig. 1 *B*) and fed it the same type of meal and examined the gastric juice obtained from the Pawlow pouch (table 1 *B*). Tables 1 *A* and 1 *B* show that there was no appreciable change either in the acidity or in the peptic activity of the gastric juice secreted by the mucosa of the fundus before or after gastro-enterostomy. There was a slight dimunition in the quantity of gastric juice secreted in the first three hours in the dog with the gastro-enterostomy.

TABLE 1 *(Dog 7).—Normal Response of Glands from Pouch*

A					B				
Normal Stomach with Pawlow Pouch (Fig. 1 A)					Gastrectomy and Pawlow Pouch (Fig. 1 B)				
(200 Gm. of Cooked Meat Given March 6, 1924)					(200 Gm. of Cooked Meat Given April 30, 1924)				
Hours	Cc. Secreted in One Hour	Free Acidity	Total Acidity	Pepsin Mm.	Hours	Cc. Secreted in One Hour	Free Acidity	Total Acidity	Pepsin Mm.
1	3.0	0.3098	0.34468	0.2	1	4.8	0.3737	0.4831	3.0
2	6.0	0.3931	0.4649	2.0	2	3.0	0.3919	0.4922	3.0
3	6.5	0.4102	0.4922	4.0	3	2.5	0.4010	0.4922	3.5

In the second series of experiments, we attempted to study the effects that the removal of the antrum may have on the change in the secretion of gastric juice.

First, we performed a Pawlow pouch (fig. 2 *A*). After the dog recuperated from the operation, we fed him a meal consisting of 200 Gm. of cooked meat and noticed the response of the Pawlow pouch (table 2 *A*). Later, we removed the antrum of the stomach and anastomosed the fundus to the duodenum (fig. 2 *B*). After the dog recuperated sufficiently from the second operation, we gave him the same meal as on the previous occasion and noticed the response of the Pawlow pouch (table 2 *B*). Tables 2 *A* and 2 *B* indicate that the acidity and the concentration of pepsin of the gastric juice was not changed after removal of the antrum. It is to be noted, however, that the quantity secreted by the pouch on the same meal, after removal of the antrum, was reduced in the first three hours to less than half of the response in the normal stomach.

We were somewhat delayed in our work, and in the meantime Smidt [16] and Portis and Portis [3] have published a report of their experiments utilizing the same methods. We did not think that it would be possible to solve all the phases of the problems concerned in our work by utilizing the Pawlow pouch method only, and we therefore proceeded to other forms of experimentation.

The third method of experimentation was based on the work of Boldyreff. [18]

This author introduced 0.5 per cent of hydrochloric acid into the stomach of a dog and found that after an hour the contents of the stomach were reduced to about 0.15 per cent hydrochloric acid. He concluded that when the acid of the contents of the stomach is raised to a certain point it is neutralized by the regurgitation of the pancreatic juice, bile and succus entericus into the stomach. Burget and Steinberg [17] repeated Boldyreff's experiments on dogs in the normal state, and have also studied the regurgitation in dogs on which gastro-enterostomy had been performed. These authors found that after gastro-enterostomy duodenal regurgitation takes place within fifteen minutes after the introduction of from 100 to 150 of 0.5 per cent hydrochloric acid 0.1 per cent in only thirty or forty-five minutes. In our present study, we have introduced 200 cc. of 0.5 per cent hydrochloric acid into the intact stomach of a dog (fig. 3 *A*) and have aspirated the

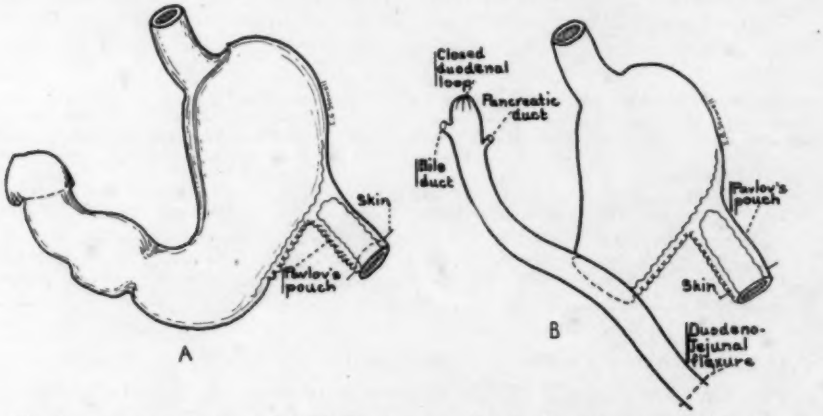

Fig. 2.—*A*, normal stomach with Pawlow pouch; *B*, Pawlow pouch with antrum removed and gastrojejunostomy.

TABLE 2 *(Dog 3).—Effects of Removal of Antrum on Secretion of Gastric Juice*

A Normal Stomach with Pawlow Pouch (Fig. 2 A) (200 Gm. of Cooked Meat Given Jan. 13, 1924)					B Antrum Resected and Pawlow Pouch Intact (Fig. 2 B) (200 Gm. of Cooked Meat Given Jan. 27, 1924)				
Hours	Cc. Secreted in One Hour	Free Acidity	Total Acidity	Pepsin Mm.	Hours	Cc. Secreted in One Hour	Free Acidity	Total Acidity	Pepsin Mm.
1	2.0	0.2371	0.3372	...	1	3.0	0.3098	0.3468	0.2
2	4.5	0.1008	0.2918	1.0	2	1.5	0.1732	0.2280	1.5
3	2.3	0.2918	0.4022	1.1	3	0.2	0.3190	0.4558	...

contents every fifteen minutes, examining them for free acidity, total acidity and visible bile. We found that it takes from an hour to seventy-five minutes for the 200 cc. of 0.5 per cent hydrochloric acid to be reduced to 0.15 per cent hydrochloric acid or less (table 3 *A*). We then performed a gatsro-enterostomy (fig. 3 *B*). After the dog recuperated sufficiently, we repeated the regurgitation experiments as

18. Boldyreff, W.: Einige neue Seiten der Tätigkeit des Pankreas, Ergebn. d. Physiol. **77**:121, 1911.

in the normal animal (table 3 *B*). After gastro-enterostomy was performed, visible bile was immediately found in the stomach and it took only about thirty or forty-five minutes for the 0.5 per cent hydrochloric acid to be reduced to 0.15 per cent hydrochloric acid or less (table 3 *B*). We then removed the antrum from the stomach of the dog, leaving the old gastro-enterostomy intact (fig. 3 *C*), and repeated the regurgitation experiments as on the normal dog (table 3 *C*). With the antrum removed, bile appeared in the contents of the stomach immediately. The 0.5 per cent hydrochloric acid was reduced to 0.14 per cent hydrochloric acid after thirty minutes, and no acid was demonstrated after forty-five minutes (table 3 *C*). The acid contents left the stomach much faster after the antrum was removed (table 3 *C*) than in the stomach in which the gastro-enterostomy only had been performed (table 3 *B*). Since the gastro-enterostomy opening was the same before and after the stomach was resected, it is difficult to explain why the process of neutralization should be much faster after the antrum was removed. It is possible that when the stomach is intact, the peristaltic

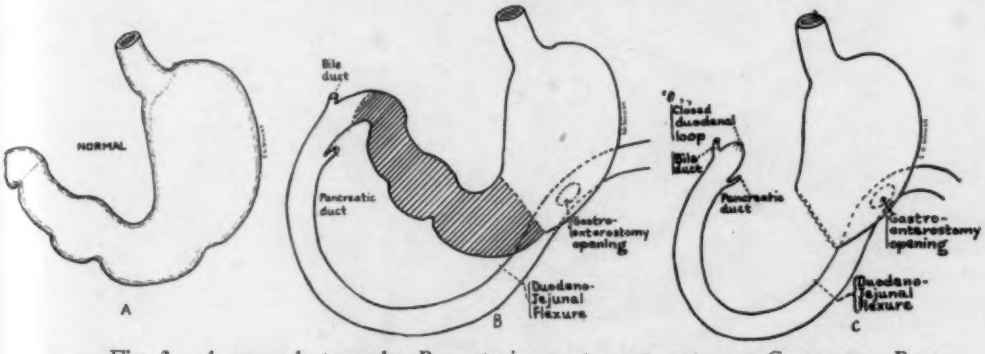

Fig. 3.—*A*, normal stomach; *B*, posterior gastro-enterostomy; *C*, same as *B*, except that the antrum has been removed.

waves propel the contents into the antrum, where they are momentarily arrested. With the antrum removed, the contents of the stomach are propelled directly into the gastro-enterostomy opening. Again, the injury to the structures involved in the performing of a gastrectomy may affect the nerve supply of the stomach to such an extent that its motor activity will be changed.

The fourth method of experimentation was as follows:

We divided the dog's stomach, separating the antrum from the fundus, in such a way that the fundus and the antrum were open to the outside by external fistulas (fig. 4). In this way the fundus was directly connected to the esophagus, and the duodenum was connected with the antrum. The dog was given nothing but milk and water and the contents of the fundus were transmitted to the antrum through a glass tube from the outside (fig. 4). After the dog recuperated sufficiently, we performed the following experiments: At first we took out the tube and washed the fundus and antrum with physiologic sodium chloride solution. We then introduced 10 Gm. of Liebigs' beef extract dissolved in 150 cc. of water into the fundus and aspirated the contents from the fundus and from the antrum every fifteen minutes (table 4 *A*). The results emphasize the fact that the fundus continuously secreted a high degree of acid, while in the antrum free acid was not found. On the following day, we took the tube out and washed the antrum and fundus with physiologic sodium chloride solution and introduced

TABLE 3 *(Dog 16 B).—Regurgitation Experiment*

A				B				C			
Normal Stomach. (Fig. 3 A)				Gastro-Enterostomy (Fig. 3 B)				Antrum Removed (Fig. 3 C)			
200 Cc. of 0.5 per Cent Hydrochloric Acid Introduced Into the Stomach at 12:40 p. m., Oct. 29, 1926				200 Cc. of 0.5 per Cent Hydrochloric Acid Introduced Into the Stomach at 12:55 p. m., Nov. 12, 1926				200 Cc. of Hydrochloric Acid Introduced Into the Stomach at 1:30 p. m., Oct. 2, 1926			
Time of Examination	Free Acidity	Total Acidity	Comment	Time of Examination	Free Acidity	Total Acidity	Comment	Time of Examination	Free Acidity	Total Acidity	Comment
12:12	0.3281	0.4558	.....	1:10	0.2006	0.2827	Bile +	1:45	0.1824	0.2644	Bile +
1:10	0.3007	0.4375	.....	1:25	0.1550	0.2280	Bile +	2:00	0.1459	0.1824	Bile ++
1:25	0.2644	0.3463	.....	1:40	0.0638	0.1459	Bile +	2:15	No free	0.0638	Bile ++++
1:40	0.0912	0.2006	Bile +	1:55	0.0456	0.1368	Bile ++	....	hydrochloric acid	.....	.....
1:55	0.0775	0.1641	Bile	2:10	0.0398	0.1276	Bile ++	....	.....	.....	.....
2:10	0.0547	0.1276	Bile	2:25	.....	0.0912	Bile ++	....	.....	.....	.....

10 Gm. of Liebigs' beef extract, in 150 cc. of water, into the antrum (fig. 4). We aspirated the contents from the antrum and from the fundus at fifteen minute intervals. From table 4 *B*, it is evident that when the beef extract was introduced into the antrum the fundus secreted free acid continuously, the highest being 0.1824, while there was no free acid in the antrum.

Lorenz and Schur [15] and Gross [12] have emphasized the importance of the antrum in the chemical phase of the secretion of gastric juice. In our experiments, we confirmed the work of Gross [12] and Krshyschkowsky [11] that when certain substances were introduced into the antrum the fundus secreted a gastric juice of considerable acidity. We have, however, also demonstrated that when certain substances are introduced into the fundus alone, the mucosa of the fundus responds with

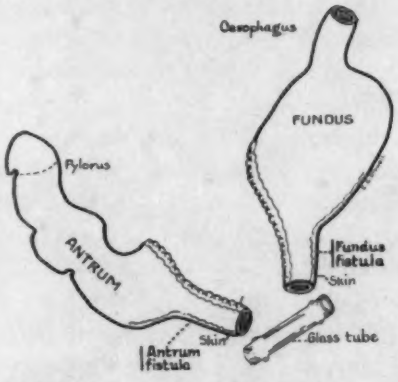

Fig. 4.—Stomach divided into antrum and fundus and both brought to the outside by means of fistulas.

TABLE 4 *(Fig. 4).—The Relation of the Antrum to the Secretion of Gastric Juice. (Fundus separated from Antrum and Both United by External Gastro-Enterostomy.)*

A: 150 Cc. of Liebigs' Beef Extract Introduced Into the Fundus at 2:00 p.m., April 6, 1927, and Both Fundus and Antrum Aspirated at Fifteen Minute Intervals			B: 150 Cc. of Liebigs' Beef Extract Introduced Into the Antrum at 6:00 p.m., April 7, 1927, and Both Fundus and Antrum Aspirated at Fifteen Minute Intervals		
	Fundus	Antrum		Fundus	Antrum
Time of Examination	Free Acidity	Free Acidity	Time of Examination	Free Acidity	Free Acidity
2:15	0.2188	None	6:15	0.1185	None
2:30	0.2736	None	6:30	0.1824	None
2:45	0.2553	None	6:45	0.1550	None
3:00	0.1185	None	7:00	0.1454	.....

a higher acidity than when the same substances are introduced into the antrum. This is contrary to the experiments of Gross [12] and Krshyschkowsky,[11] who claim that the introduction of substances into the fundal part of the stomach does not bring about the secretion of gastric juice.

In the previous series of experiments, we were able to demonstrate that after the antrum was resected, the fundus secreted gastric juice of normal acidity, though it was less in amount (tables 2 *A* and 2 *B*). When certain substances were introduced into the antrum (fig. 4), the fundus secreted a gastric juice lower than normal in acid concentration (table 4 *B*). In the experiments in regurgitation (figs. 3 *A*, 3 *B* and 3*C* and tables 3 *A*, 3 *B* and 3 *C*), we found that the removal of the antrum causes a rapid emptying of the contents of the stomach and a decisive and almost immediate neutralization of these contents through the regurgitation of the intestinal juices. It remained to be determined which factors are more important in bringing about the change in the chemistry of the contents of the stomach. Does a gastrectomy eliminate what is known as the chemical phase of secretion of gastric juice, or does it change the anatomic and physiologic factors in such a way as to bring about the reduction in acidity by the neutralization through the influx of the intestinal contents?

We performed the regurgitation experiments (table 5 *A*), and also gave the animal a test meal containing 20 Gm. of Liebigs' beef extract diluted in 300 cc. of water (table 6 *A*). After finding out the response to the intact stomach (fig. 5 *A*, tables 5 *A* and 6 *A*), we resected the antrum and administered the same test meals as in the experiment on the normal stomach (fig. 5 *B*, tables 5 *B* and 6 *B*).

After the dog had sufficiently recuperated from the operation for the resection of the antrum (fig. 5 *B*), we divided the duodenum at the point above the anastomosis and united the distal part of the duodenum with the ileum.[19] In this way, all the pancreatic juice and bile were directly transmitted to the ileum and could not regurgitate into the fundus of the stomach (fig. 5 *C*).

In the regurgitation experiments, after the stomach was resected, the neutralization took place rapidly (table 5 *B*). After the duodenal contents were diverted to the ileum, a high acidity persisted until no more acid contents could be obtained from the stomach (table 5 *C*). The same result, only not so striking, is apparent from tables 6 *A* and 6 *B*, in which the animal was given a meal containing 20 Gm. of Liebigs' beef extract dissolved in 300 cc. of water. Table 6 *A* showed that after this meal was given the normal stomach responded with the usual acidity of the contents of the stomach (free acid, from 0.1003 to 0.2188). After the stomach was resected and the duodenal contents diverted (fig. 5 *C*,

19. The method of diverting the duodenal contents into the ileum is original with us and was suggested by the senior author to Professor Burget of the Physiology Department of the University of Oregon Medical School six years ago. We intended to employ this method for the purpose of studying the etiology of duodenal and gastric ulcers. Since then, however, Mann has published his work utilizing the same principle, Ann. Surg. **77**:409, 1923.

TABLE 5 *(Dog 40 B).—Regurgitation Experiment*

A — Normal Stomach (Fig. 5 A)				B — Antrum Removed (Fig. 5 B)				C — Antrum Removed and Duodenal Contents Diverted to the Ileum (Fig. 5 C)			
200 Cc. of Hydrochloric Acid Introduced Into Stomach at 1:00 p. m., May 16, 1927				200 Cc. of 0.5 per Cent Hydrochloric Acid Introduced Into the Stomach at 1:15 p. m., June 1, 1927				200 Cc. of 5.0 per Cent Hydrochloric Acid Introduced at 1:15 p.m. June 10, 1927			
Time of Examination	Free Acidity	Total Acidity	Comment	Time of Examination	Free Acidity	Total Acidity	Comment	Time of Examination	Free Acidity	Total Acidity	Comment
1:15	0.2736	0.4375	.....	1:30	0.2280	0.3008	.....	1:30	0.3372	0.4102	None
1:30	0.2553	0.3554	.....	1:45	0.2280	0.2736	.....	1:45	0.2553	0.3046	None
1:45	0.2553	0.3463	.....	2:00	0.1276	0.1824	Bile ++	2:00	0.2371	0.3372	None
2:00	0.2462	0.3190	.....	2:15	0.0729	0.0912	Bile +++	2:15	0.2462	0.3463	None
2:15	0.1915	0.3094	Bile +	2:30	.....	0.0825	Bile ++	2:30	0.2371	0.3281	None
2:30	0.1641	0.2553	Bile +	....	.....	.....	.....	2:45	No more stomach contents.		

table 6 *C*), and the dog was given the same meal consisting of Liebigs' beef extract, a free acidity that was higher than that in the intact stomach persisted for a long time (free acidity, from 0.1915 to 0.2736).

It is evident that when the antrum is resected and the pancreatic juice and bile are diverted to the ileum (fig. 5 *C*) and the dog is given a standard meal, there is a constant free acidity, in spite of the fact that the antrum is totally removed. Without doubt, this demonstrates that after the antrum is removed, the changed chemistry of the contents of the stomach is chiefly due to the regurgitation of the alkaline juices of the duodenum into the stomach.

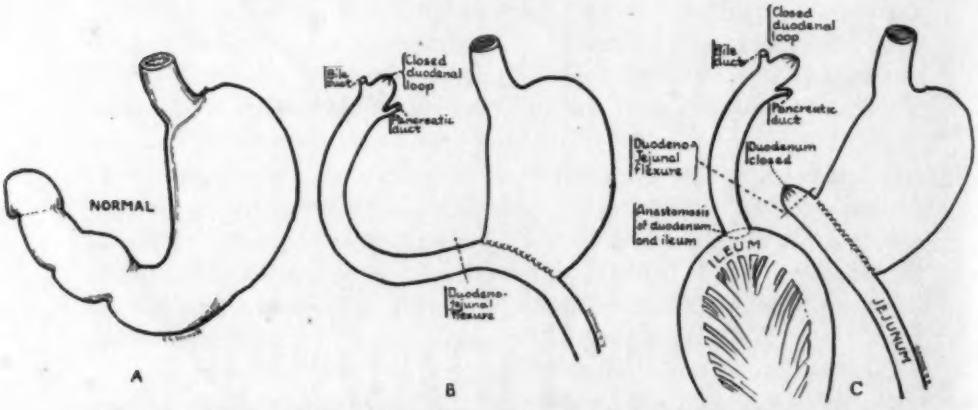

Fig. 5.—*A*, normal stomach; *B*, antrum removed and fundus anastomosed to the jejunum; *C*, same as *B*, except that the duodenum has been divided above the anastomosis and united to the ileum. The duodenal contents are emptying directly into the ileum.

TABLE 6 *(Dog 40 B).—Test Meal Experiment*

A Normal Stomach (Fig. 5 A)			B Antrum Removed (Fig. 5 B)			C Antrum Removed and Duodenal Contents Diverted to the Ileum (Fig. 5 C)		
20 Gm. of Liebigs' Beef Extract in 300 Cc. of Water Given at 12:45 May 18, 1927			20 Gm. of Liebigs' Beef Extract in 300 Cc. of Water Given at 10:25 a.m., May 31, 1927			20 Gm. of Liebigs' Beef Extract in 300 Cc. of Water Given at 9:30 a. m., July 1, 1927		
Examination	Free Acidity	Total Acidity	Examination	Free Acidity	Total Acidity	Examination	Free Acidity	Total Acidity
1:00	0.1459	0.2462	10:40	0.1824	0.2736	9:45	0.2553	0.4010
1:15	0.1185	0.2371	10:55	0.1459	0.2371	10:00	0.2553	0.4010
1:30	0.1824	0.2736	11:10	0.1641	0.2462	10:15	0.2462	0.3372
1:45	0.1915	0.3372	11:25	0.1185	0.2344	10:30	0.2553	0.3372
2:00	0.2188	0.3554	11:40	0.1641	0.3007	10:45	0.2736	0.3919
2:15	0.1732	0.3190	11:55	0.1185	0.1915	11:00	0.2188	0.3372
2:30	0.1550	0.2918	12:10	0.1368	0.2188	11:15	0.2097	0.2918
2:45	0.1185	0.1824	12:25	0.1094	0.1732	11:30	0.2006	0.2827
3:00	0.1003	0.1185	.....	.....	.....	11:45	0.1915	0.2736
....	.....	.....	.....	.....	.....	12:00	No more could be aspirated	

CONCLUSIONS

1. After a gastro-enterostomy is performed, the secretion of gastric juice remains of the same concentration in acidity, but, as shown by the Pawlow pouch method, the amount of secretion is slightly lessened. The contents of the stomach are neutralized to a certain extent by the regurgitation of the intestinal contents.

2. We have been able to demonstrate that when the fundus is separated from the antrum and various substances are introduced into the fundus, the glands of the fundus respond with the secretion of gastric juice of high acidity. This is contrary to the observations of Krshyschkowsky,[11] Gross,[12] and Zeljony,[13] who stated that irritation of the surface of the fundal mucosa of the stomach does not bring forth the secretion from its glands.

3. After the antrum is removed, free acidity of the contents of the stomach is considerably reduced or is entirely absent. The mechanism concerned in this process is due to two factors The removal of the antrum eliminates a part of the stomach from which surface absorbtion of foodstuffs stimulates the secretion from the fundal glands. The biggest factor in the reduction of acidity after resection of the stomach is the neutralization of the contents of the stomach by the influx of the alkaline juices from the intestine. We have demonstrated this definitely, since after the antrum is removed and the bile and pancreatic juice are diverted to the ileum the acidity in the fundus is high and persists for a long time.

4. The stomach is usually divided into two distinct parts: the proximal, which is the largest and which is spoken of as the fundus and corpus, lined by the fundus glands which secrete acid and pepsin; the distal, or the smallest part, which is spoken of as the antrum or pars pylorica. This part is lined by the pyloric glands which do not secrete acid. It is therefore contrary to all physiologic and anatomic facts for surgeons and clinicians to state that by removing the antrum the area of the stomach secreting acid is also removed.

MECHANISM AND TREATMENT OF EXPERIMENTAL SHOCK

I. SHOCK FOLLOWING HEMORRHAGE*

ALFRED BLALOCK, M.D.
NASHVILLE, TENN.

DEFINITION

Many syndromes are grouped by investigators and clinicians under the general term "shock." Since the word has various connotations for different persons, it might well be discarded from medical nomenclature. However, no satisfactory synonym is available, and the widespread clinical use of the term seems to warrant its retention.

Throughout this and subsequent publications, "shock" is used to denote a condition of acute circulatory failure characterized by prostration, apathy or stupor, tachycardia with feeble, regular pulse and, in many instances, diminished blood pressure. The temperature of the body is often subnormal. Pallor and slight cyanosis are usually present. Edema, visceral congestion and accumulations of fluid in the serous cavities do not occur in shock. The latter signs are characteristics of chronic circulatory failure ("cardiac decompensation," "congestive failure," etc.). Much confusion has resulted from a lack of complete differentiation between these two general conditions, which not only are different as to chronicity and etiology, but, as will be demonstrated, are dissimilar in regard to pathologic physiology and response to treatment.

INTRODUCTION

Shock is generally recognized to be a group of symptoms and not a disease. This syndrome is encountered more often than any other in surgical patients. The more common causes of clinical shock are the following: (1) acute hemorrhage, (2) prolonged anesthesia, (3) extensive wounds, (4) any acute infection in the terminal stages, (5) pulmonary embolism, (6) coronary occlusion, (7) collapse caused by heat, (8) excessive manipulation of abdominal viscera at operation, (9) fractures of long bones and (10) moribund states from any cause. Among the more important procedures which may produce experimental shock are (1) the administration of histamine, (2) the intravenous administration of fat and (3) excessive hyperventilation of the lungs.

In spite of the many important investigations of shock, particularly of the traumatic type, which have been made in the past ten years, the disturbances of circulatory function are poorly understood, and present

* From the Department of Surgery, Vanderbilt University Medical Department.

methods of treatment leave much to be desired. Most of the studies have been primarily concerned with blood pressures. Such observations as have been made on the cardiac output have been carried out in most instances by plethysmographic methods, which in themselves tend to produce shock and hence are relatively valueless for the purpose. Aub and Cunningham,[1] however, using the Fick method, found a marked reduction in cardiac output, as well as a reduction in blood pressure, in experimental traumatic shock. Blalock and Harrison[2] observed a similar reduction in cardiac output after hemorrhage, but did not determine blood pressures.

The purposes of the present series of investigation have been: (1) to attempt a determination of the relative importance of failure of the several circulatory functions in the more common and important types of shock, under conditions approximating clinical states as closely as possible; and (2) to attempt an evaluation of the various methods of treatment on the basis of these functional disturbances.

Shock produced by hemorrhage has been studied first, because of its clinical importance, and because it is almost the only type of shock for which there is a specific treatment (transfusion), against which various other therapeutic measures can be evaluated.

METHOD

Dogs of various sizes were used. Morphine was employed as an anesthetic. Although this drug may cause changes in cardiac output, as Tappan and Torrey[3] have shown, the change is less marked than that produced by urethane (Tappan and Torrey), ether (Blalock[4]) or chloroform (Blalock[5]), and is less inconstant than that produced by barbital (Harrison, Wilson and Pilcher[6]). Furthermore, the minute cardiac output of the morphinized dog is not altered by changes in rate dependent on variations in vagal tone (Tappan and Torrey), and in this respect it is similar to the minute cardiac output of the trained unnar-

1. Aub, J. C., and Cunningham, T. D.: Studies in Experimental Traumatic Shock—Oxygen Content of the Blood, Am. J. Physiol. **54**:408, 1920.

2. Blalock, A., and Harrison, T. R.: The Regulation of Circulation: V. The Effect of Anemia and Hemorrhage on the Cardiac Output of Dogs, Am. J. Physiol. **80**:157, 1927.

3. Tappan, V., and Torrey, E. H.: Studies on the Cardiac Output of the Dog: III. Influence of Pulse Rate upon Minute Volume Under Anesthesia, Am. J. Physiol. **78**:376, 1926.

4. Blalock, A.: Cardiac Output in the Dog During Ether Anesthesia, Arch. Surg. **14**:732 (March) 1927.

5. Blalock, A.: The Effects of Ether, Chloroform and Ethyl Chloride Anesthetics on the Cardiac Output and Blood Pressure, Surg. Gynec. Obst., to be published.

6. Harrison, T. R.; Wilson, C. P., and Pilcher, C.: Personal communication to the author.

cotized dog (Marshall[7]). Finally, the cardiac output of the morphinized dog may be constant for a period of hours (Harrison and Leonard[8]) after an initial decrease within the first two hours (Tappan and Torrey).

Although morphine has seemed to be the least undesirable anesthetic for the purpose, there are some objections to its use, as it causes slowing of the pulse and may alter the response of the circulation to various abnormal states (Harrison, Wilson and Blalock;[9] Marshall[10]). For this reason a few experiments have been done on trained unnarcotized animals.

The dogs were given the drug (from 4 to 6 mg. per kilogram of body weight) from two to six hours before the start of the experiment. The mean blood pressure was measured by a cannula in the femoral artery. The oxygen consumption was determined with the Benedict spirometer, the Roth graphic recording device being used. Samples of blood were drawn from the right and left ventricles, with the usual precautions against contamination with air, and analyzed in duplicate for oxygen content in the Van Slyke-Neill manometric blood gas apparatus (some of the samples of arterial blood were obtained from the femoral artery). The cardiac output was calculated from the Fick formula:

$$\frac{\text{Cc. oxygen consumed per minute}}{\text{Cc. oxygen taken up by cc. of blood in passing through the lungs}} = \text{Cc. of blood passing through the lungs per minute}$$

(It should be emphasized that the animals were not subjected to any operative procedure other than the insertion of an arterial cannula and repeated punctures of the heart. The absence of manipulative shock is believed to be important in the proper study of hemorrhagic shock).

After one or more control determinations of cardiac output, the animal was bled from the femoral artery. The amount of blood withdrawn varied in different experiments. In many instances several determinations of minute cardiac output were made after several successive bleedings. In most of the experiments a sufficient number of observations was made to allow the drawing of definite conclusions as to whether the fall in blood pressure occurred before or after the fall in minute cardiac output.

When a typical state of shock—with tachycardia, diminished mean blood pressure and decreased cardiac output—had been reached, a therapeutic procedure was instituted, and its effect on pulse rate, mean blood pressure and minute cardiac output was then determined. It was considered unwise to use two or more methods of treatment at the same time, as the evaluation of their relative importance would have then been difficult. The following therapeutic measures were employed in various experiments:

A. *Transfusion.*—In seven experiments sodium citrate was added to the blood which was removed, and transfusion into the femoral vein was carried out after

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7. Marshall, E. K., Jr.: Studies on the Cardiac Output of the Dog: I. The Cardiac Output of the Normal Unanesthetized Dog, Am. J. Physiol. **77**:459, 1926.

8. Harrison, T. R., and Leonard, B. W.: The Action of Digitalis on the Cardiac Output of Dogs, J. Clin. Investigation **3**:1, 1926.

9. Harrison, T. R.; Wilson, C. P., and Blalock, A.: The Effects of Changes in Hydrogen Ion Concentration on the Blood Flow of Morphinized Dogs, J. Clin. Investigation **1**:547, 1925.

10. Marshall, E. K., Jr.: Studies on the Cardiac Output of the Dog, Influence of Atropin and Carbon Dioxide on the Circulation of the Unanesthetized Dog, J. Pharmacol. & Exper. Therap. **29**:167, 1926.

the state of shock had been induced. The transfusion was usually done in several stages, the animal being studied after various fractions of the withdrawn blood had been restored. (Seven experiments were performed, including forty-eight determinations of cardiac output.)

B. *Drugs.*—The drugs used were as follows:

1. Digitalis was administered—from 0.25 to 0.5 cc. per kilogram intravenously. The minute cardiac output was determined at intervals of from twenty minutes to two hours after the drug was administered. (Five experiments were performed, including fifteen determinations of minute cardiac output.)

2. Strychnine was administered as strychnine sulphate—from 0.5 to 0.8 mg. per kilogram—intravenously or subcutaneously. The minute cardiac output was determined from six to twenty-five minutes after intravenous administration, and from fifteen minutes to one hour after the subcutaneous administration of the drug. (Five experiments were performed, including fifteen determinations of minute cardiac output.)

3. Ether was used, because I[4] have demonstrated that ether anesthesia causes an increased minute cardiac output in normal dogs and morphinized dogs. Ether was administered in doses of from 0.14 to 0.23 cc. per kilogram, intramuscularly in three experiments and intra-arterially in five experiments. The latter method was used because Ranson, Windle and Faubion[11] found that intra-arterial injections of ether were safer than intramuscular injections. Blood samples were drawn from five to twenty minutes after the drug had been given. In several instances a rapid intravenous injection of ether was followed by immediate death of the animal, this occurring before observation on the circulation could be made. (Eight experiments were performed, including twenty-three determinations of cardiac output.)

4. Caffeine was administered as caffeine sodium benzoate in doses of from 4 to 65 mg. per kilogram. The determinations of cardiac output were made at various intervals—from three to forty minutes after intravenous doses, and from seven to forty minutes after subcutaneous doses. (Eight experiments were performed, including twenty-nine determinations of cardiac output.)

5. Epinephrine hydrochloride was given intravenously or subcutaneously—from 0.05 to 0.18 mg. per kilogram. The circulatory measurements were carried out at time intervals of from two to forty-five minutes after the administration of the drug. (Seven experiments were performed, including twenty-three determinations of cardiac output.)

6. Ephedrine was administered as the hydrochloride. The drug was given subcutaneously, the dose being 2 mg. per kilogram. (Three experiments were performed, including fourteen determinations of cardiac output.)

C. *Saline Infusion.*—Physiologic sodium chloride solution was administered intravenously in seven experiments. The total amount administered varied from 13 to 40 cc. per kilogram. The observations were made at various time intervals—from four minutes to five hours—in the different experiments after the infusion. (Seven experiments were performed, including eighteen determinations of cardiac output.)

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11. Ranson, S. W.; Windle, W. F., and Faubion, L. R.: Vasodilator Mechanisms: V. The Intra-Arterial Injection of Ether, Am. J. Physiol. **64**:320, 1923.

RESULTS

As the results in the morphinized animals and the trained animals were similar, the two groups are presented together.

The Effects of Bleeding (tables 1 and 2; charts 1, 2, 3 and 11).—The different animals varied in the degree of resistance to hemorrhage.

TABLE 1.—*Effects of Hemorrhage on Circulation*

		Before Bleeding				After Bleeding					
Experiment	Weight, Kg.	Pulse Rate	Oxygen Consumption per Minute, Cc.	Mean Blood Pressure, Mm. Mercury	Cardiac Output per Minute, Cc.	Time After Last Bleeding, Minutes	Total Amount Bled, Cc. per Kg.	Pulse Rate	Oxygen Consumption per Minute, Cc.	Mean Blood Pressure, Mm. Mercury	Cardiac Output per Minute, Cc.
1	16	50	136.8	120	2,330	35	33	120	147.6	110	1,890
						20	44	180	124.2	100	1,240
2	19	80	151.1	112	2.520						
		84	167.4	116	2,460	5	21	152	150.2	118	1,800
						20	21	176	150.2	116	1,460
3	13.7	64	82.3	106	2,080	60	20	40	85.0	96	1,940
						10	30	92	87.8	104	1,020
						120	30	192	95.7	93	1,170
4	18	100	140.4	124	4.250	4	22	145	165.6	114	2,460
						120	22	150	158.4	120	3,180
						4	32	195	158.4	88	1,886
						40	32	180	165.6	72	1,440
						85	32	195	180.0	78	1,600
5	8.5	54	79.2	98	1,240	5	23	180	84.6	88	930
						25	23	176	104.4	88	1,060
						63	23	175	72.0	97	720
						5	35	200	50.4	36	390
						18	35	200	37.8	18	370
6	15	54	136.8	122	2,480	1	23	120	144.0	118	2,500
						19	23	125	140.4	128	1,920
						3	30	180	144.0	104	1,210
						35	30	200	108.0	70	830
7	11.8	56	90.0	108	1,970	3	20	68	91.8	105	1,590
						31	20	66	93.0	96	1,440
						4	39	150	100.8	70	1,200
						23	39	150	86.4	79	910
8	17	64	101.2	127	2,610	15	20	84	127.0	122	1,770
		92	103.0	140	2,750	40	20	100	145.6	126	2,270
						5	30	92	134.3	118	1,710
						40	30	190	150.0	118	2,030
						10	40	230	150.0	102	1,360
9*	13	90	117.0	106	2,710	25	27	95	109.8	99	1,340
						20	37	180	100.8	79	1,150
						25	47	150	102.6	40	860
10*	11*	88	109.2	119	2,350	20	12	150	118.4	92	1,620
						65	12	168	99.9	108	1,490
						70	22	192	100.2	76	1,240
11	9.5	88	96.9	130	2,020	16	21	88	83.6	123	1,310
						36	21	92	85.5	119	1,210
						1	24	118	89.3	118	1,260
						1	27	185	91.2	107	1,100
						1	30	205	93.1	112	1,020
						1	33	200	91.2	92	850
						80	35	200	87.4	55	750

* Trained unnarcotized dog.

Ordinarily, bleeding up to 15 cc. per kilogram did not cause any striking change in the general condition. Evidence of shock, as manifested by tachycardia and slight stupor, was first noted when from 20 to 30 cc. of blood per kilogram had been removed. The withdrawal of amounts greater than 40 cc. per kilogram was usually followed by death

in a relatively short time. The animals could survive greater loss of blood when they were bled slowly than when the hemorrhage was rapid. They tended to recover rapidly from mild shock, but severe shock once induced was usually progressive and fatal, even if no further bleeding was done.

The pulse rate was increased. Respiratory cardiac arrhythmias disappeared. The breathing was usually not altered until shock became extreme, when rapid and shallow breathing sometimes occurred. The arterial oxygen content was diminished, but not in great degree in most experiments, the usual change being from 1 to 3 per cent by volume, corresponding to a diminution in hemoglobin of from 5 to 15 per cent. These results are in general similar to those of Blalock and Harrison [2] in their observations on hemorrhage.

The consumption of oxygen was often slightly increased after the initial bleedings, but was diminished in the more severe stages of shock.

The mean blood pressure was not significantly diminished until relatively large amounts of blood had been withdrawn. During and at the conclusion of a small bleeding the pressure was sometimes slightly below normal, but a rapid return to the normal level was the rule. (In considering changes in blood pressure, cardiac output and pulse rate, all values within 10 per cent of that during the control period have been considered as within the normal limits.) Of twenty-eight observations on animals which had been bled between 20 and 30 cc. per kilogram, the mean blood pressure was normal in twenty; nineteen measurements on animals which had been bled more than 30 cc. and less than 40 cc. per kilogram, the mean pressure was reduced in fifteen. In every instance in which more than 40 cc. of blood per kilogram had been withdrawn, the mean pressure was reduced. When the mean pressure once started to diminish, a rapid decline was the rule, even though the succeeding bleedings were of small magnitude. A dog weighing 10 Kg. which had exhibited a decline of only 10 mm. of mercury after being bled 300 cc. might show a diminution of an additional 40 mm., after losing an additional 30 cc. of blood. These observations are in accord with Porters [12] conception of a "critical level of blood pressure," and indicate that 30 cc. per kilogram is, for most dogs, approximately the "critical" amount of blood which can be lost without consequent severe shock.

Tachycardia always preceded the fall in blood pressure. The relative stability of the blood pressure despite large hemorrhage was one of the most striking features of the experiments.

The minute cardiac output was always diminished after hemorrhage. The degree of diminution was well beyond the limits of error of the

12. Porter, W. T.: Traumatic Shock from Fat Embolism of the Vasomotor Center, Am. J. Physiol. **71**:277, 1925.

method (from 5 to 8 per cent) in every instance except two. Loss of from 15 to 20 cc. of blood per kilogram was regularly followed by decreased minute cardiac output; a loss of 30 cc. per kilogram was usually necessary to produce a drop in mean blood pressure. Diminution in the mean blood pressure did not precede the decline in cardiac output in any experiment; the reverse was always the case. The minute cardiac output was usually diminished by more than one-third, and often by more than one-half, before a significant (greater than 10 per cent) decline in mean blood pressure occurred.

Ordinarily, the diminution in minute cardiac output was associated with an increase in pulse rate, the stroke output being, therefore, greatly diminished. In those experiments in which repeated observations were made during small successive bleedings, it was found that the minute cardiac output diminished before the pulse rate increased significantly. This relationship was noted in four experiments, whereas the change in pulse rate preceded the change in minute output in only one experiment.

The temporal relationships between the three circulatory factors is well illustrated in charts 1, 2, 3 and 11. As can be seen, the first striking change with hemorrhage is the diminution in minute cardiac output. The second change is in the pulse rate, which increases. The fall in mean blood pressure occurs last.

The Effects of Various Therapeutic Measures.—Transfusion: The results of this procedure are presented first for the sake of comparison with the other forms of treatment, and are shown in table 2 and chart 3. When the degree of shock was not extreme, the animal could be readily restored to a relatively normal condition by the infusion of from one half to two thirds of the amount of blood which had been withdrawn. The results of transfusion, even if all the blood was replaced, were considerably less satisfactory in those animals which had reached a state of severe shock. In such instances, transfusion produced temporary improvement, but the animal often died from one to two hours later.

The consumption of oxygen was usually increased above the shock level and often above the original control level. This indicates that an oxygen debt may be present in shock; this will be discussed later.

The pulse rate did not return to normal after transfusion in any experiment. Only a slight degree of slowing was produced. The usual pulse rates were from 180 to 220 before transfusion and from 160 to 200 after transfusion.

The mean blood pressure was increased above the preceding level by the administration of blood, but usually did not reach the normal value for the animal. After a small transfusion, the rise was poorly sustained and was followed by a secondary decline, but when larger amounts of blood were given the pressure remained above the shock level, except

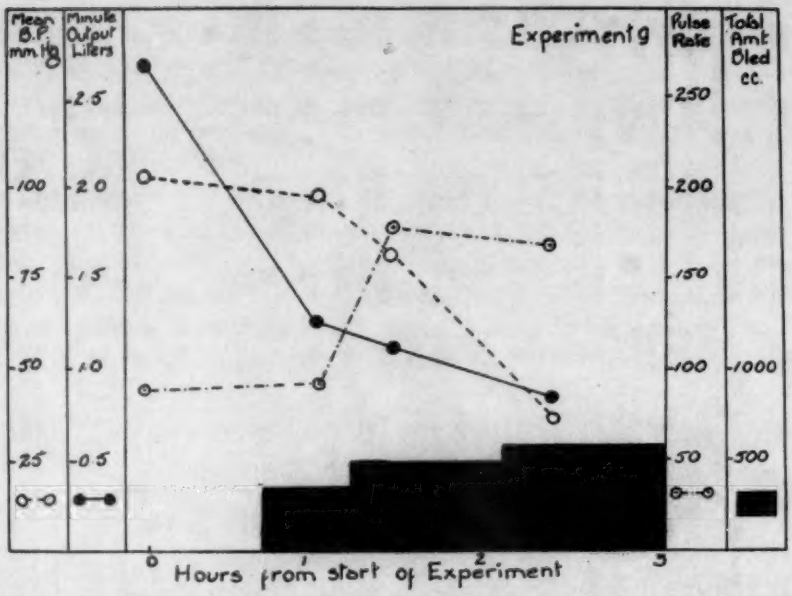

Chart 1.—Effects of hemorrhage on circulation in a trained unnarcotized dog. First the minute cardiac output diminished, then the pulse rate increased and finally the blood pressure decreased. The animal was not given any general anesthetic or narcotic and had previously been trained to the method.

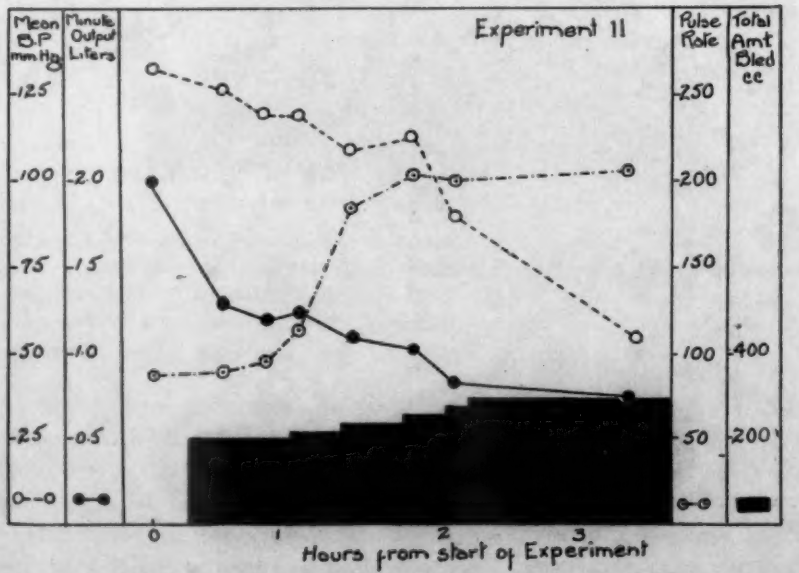

Chart 2.—Effects of hemorrhage on circulation in a morphinized dog. The usual temporal relationships are shown, the minute output decreasing first, the pulse rate increasing next and the mean blood pressure not showing any striking decline until the minute output was more than 50 per cent below normal.

TABLE 2.—*Effect of Bleeding and Transfusion on Circulation of Dogs*

		Before Bleeding				After Bleeding			Before Transfusion			After Transfusion					
Experiment	Weight, Kg.	Pulse Rate	Oxygen Consumption per Minute, Cc.	Mean Blood Pressure, Mm. Mercury	Cardiac Output per Minute, Cc.	Time After Last Bleeding, Minutes	Total Amount Bled, Cc. per Kg.	Pulse Rate	Oxygen Consumption per Minute, Cc.	Mean Blood Pressure, Mm. Mercury	Cardiac Output per Minute, Cc.	Time After Last Transfusion, Minutes	Total Amount Transfused, Cc. per Kg.	Pulse Rate	Oxygen Consumption per Minute, Cc.	Mean Blood Pressure, Mm. Mercury	Cardiac Output per Minute, Cc.
12	7	60	69.5	88	1,480	10	25	210	54.0	98	960	7	17	160	60.4	95	1,450
						5	34	204	34.8	45	600	5	22	180	43.9	66	800
13	10	48	73.1	83	2,160	10	13	76	70.3	85	1,070						
						5	23	240	68.5	12	690	15	12	148	62.9	54	930
												20	22	108	66.6	73	1,140
14*	11	..	.....	108	.....	12	45	155	114.0	50	1,090						
						20	45	180	114.0	48	1,130	1	8	180	152.0	70	2,080
												1	18	180	163.4	74	2,960
												1	45	180	159.6	86	4,030
												15	45	180	159.6	98	3,800
15*	11	88	109.2	119	2,350												
						70	20	192	100.2	76	1,240						
						165	20	220	109.1	52	1,140	20	10	210	107.3	74	1,400
												60	10	215	77.7	48	800
16	16	60	138.6	94	2,280	15	51	220	133.2	66	1,220	20	25	160	140.4	97	2,160
						35	64	230	129.6	69	1,130						
						120	64	250+	179.2	44	1,160	15	62	180	215.8	114	3,520
17	13.2	68	112.2	114	2,770												
		68	109.6	116	2,940	30	30	200	92.2	28	1,400	10	16	168	104.4	76	2,640
												35	16	176	95.7	77	1,420
												65	16	200	109.9	77	1,630
18	10	70	86.7	102	1,810												
		72	83.1	105	1,730	20	30	78	71.3	102	940						
						15	33	84	73.6	101	970						
						20	37	120	76.0	106	860						
						20	40	160	80.8	103	870						
						20	44	180	90.3	96	770						
						70	47	190	86.9	44	610	1	12	180	102.1	70	870
												1	21	180	122.3	90	1,400
												1	32	180	114.0	64	1,620
												1	35	180	110.4	68	1,700
												40	35	180	109.3	76	1,300
												140	35	200	104.5	80	1,670
												185	35	190	103.3	77	1,510

* Trained unnarcotized dog.

in those instances in which the dog was moribund before transfusion was instituted. In several experiments, the infusion of blood was begun when the animal was dying from respiratory failure; but beneficial effects were not achieved, even when artificial respiration was also administered.

The minute cardiac output was increased in every instance. The degree of increase was directly proportional to the amount of blood replaced and inversely proportional to the degree of shock. Twenty-two determinations of cardiac output were made after transfusion. In eleven of these, the minute output was below the original normal value; in eight instances, an approximately normal level had been reached,

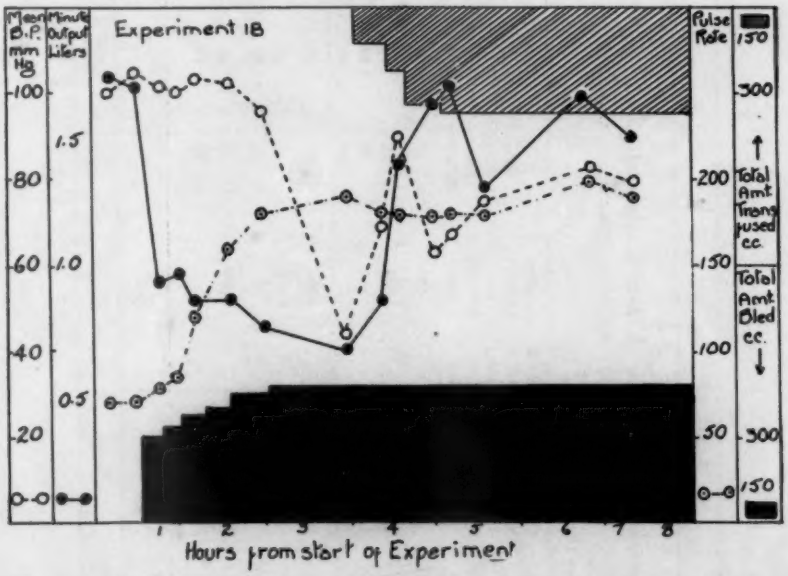

Chart 3.—Effects of hemorrhage and transfusion on circulation. The usual effects of successive bleedings are shown. Transfusion caused the blood pressure to rise first. The minute output returned to above the normal level after all the blood withdrawn had been replaced. Transfusion had practically no effect on the pulse rate.

whereas in three the minute output after transfusion was greater than that before bleeding. The stroke output was always increased by transfusion, but it did not approach the normal value because the pulse rate remained rapid.

The effect of transfusion on minute cardiac output was usually permanent if the animal had been in a mild state of shock, but always temporary if the condition was poor before blood was replaced. In the latter instances, the minute output tended to diminish following the immediate rise after transfusion. When the amount of blood restored

TABLE 3.—*Effect of Digitalis on Circulation of Dogs in State of Shock Produced by Hemorrhage*

		Before Digitalis						After Digitalis					
Experiment	Weight, Kg.	Time After Bleeding, Minutes	Total Amount Bled, Cc. per Kg.	Pulse Rate	Oxygen Consumption per Minute, Cc.	Mean Blood Pressure, Mm. Mercury	Cardiac Output per Minute, Cc.	Time After Drug, Minutes	Total Amount of Drug Given, Mg. per Kg.	Pulse Rate	Oxygen Consumption per Minute, Cc.	Mean Blood Pressure, Mm. Mercury	Cardiac Output per Minute, Cc.
20	5.7	120	42	190	73.8	80	820	17	53	144	64.8	80	600
21	16	35	22	200	121.6	76	1,180	35	28	190	125.4	58	1,070
								70	28	200	125.4	43	990
								105	28	210	129.2	36	1,070
22	13	30	40	190	129.2	85	1,460	20	31	200	121.6	75	1,430
23	11	120	40	190	87.4	30	680	8	37	185	106.4	42	820
								21	37	195	77.9	32	600
24*	9	60	39	180	87.4	54	1,060	20	44	190	72.2	48	600
								25	44	190	72.2	48	550

* Trained unnarcotized dog.

approached the amount withdrawn, the minute cardiac output usually remained at an approximately normal level. After smaller transfusions there was an initial rise and then a fall in the minute output, which, however, remained above the pretransfusion level.

In general, the effect of the restoration of blood was more marked on the minute cardiac output than on the blood pressure. In this respect transfusion and bleeding were similar.

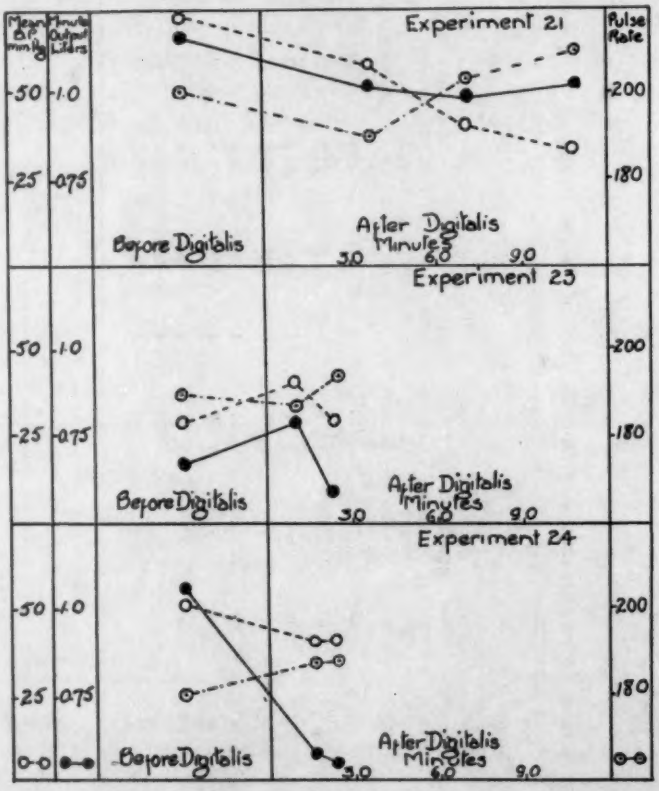

Chart 4.—Effect of digitalis on circulation of dogs in a state of hemorrhagic shock. Digitalis caused a diminished minute output in each instance. In one of the three experiments there was a slight initial rise in this function. The blood pressure was not increased by the drug and practically no effect on pulse rate was observed.

The effects of removing and replacing blood on the circulation may be summarized as follows: Repeated bleeding causes a diminution in cardiac output, followed by an increase in pulse rate, which is succeeded by a fall in mean blood pressure. Transfusion causes each of these factors to return toward normal, but the effect is greatest on the cardiac output and least on the pulse rate, the blood pressure being intermediate.

TABLE 4.—*Effect of Strychnine on Circulation of Dogs in State of Shock Produced by Hemorrhage*

		Before Strychnine						After Strychnine						
Experiment	Weight, Kg.	Time After Bleeding, Minutes	Total Amount Bled, Cc. per Kg.	Pulse Rate	Oxygen Consumption per Minute, Cc.	Mean Blood Pressure, Mm. Mercury	Cardiac Output per Minute, Cc.	Time After Giving Drug, Minutes	Total Amount of Drug Given, Mg. per Kg.	Pulse Rate	Oxygen Consumption per Minute, Cc.	Mean Blood Pressure, Mm. Mercury	Cardiac Output per Minute, Cc.	Method of Administration
25*	8	30	25	180	50.4	35	630	35	5	210	46.8	40	400	Intramuscular
26	12	20	30	135	122.4	60	1,680	6	5	160	97.2	63	1,160	Intravenous
27	13	20	35	175	119.6	77	1,530	16	3	180	125.4	73	1.470	Subcutaneous
								76	3	190	129.2	84	1,460	
28	11	60	40	150	98.1	104	1,000	15	4	75	98.8	104	1,110	Subcutaneous
								37	4	80	117.8	104	1,190	
29*	14	180	28	180	106.7	60	1,200	7	4	200	110.6	58	1,330	Subcutaneous
								23	4	210	115.7	60	1.320	
								55	4	210	115.7	55	1.420	

* Trained unnarcotized dog.

Drugs: 1. Digitalis. Inspection of table 3 and chart 4 demonstrates that digitalis when given in "therapeutic" amounts is harmful in shock.

The pulse rate was diminished in one instance and unchanged in eight observations after the drug was given. The mean blood pressure was increased once, unchanged twice and diminished in six determinations. In one experiment the minute cardiac output showed an initial rise, followed by a fall. In the remaining experiments, the drug produced a diminution in minute cardiac output. The degree of decrease varied from 2 to 45 per cent, and was in general proportional to the amount of the drug given. These observations confirm the results of Harrison and Leonard,[8] who observed diminished cardiac output after the use of digitalis in normal dogs, and who concluded that the drug

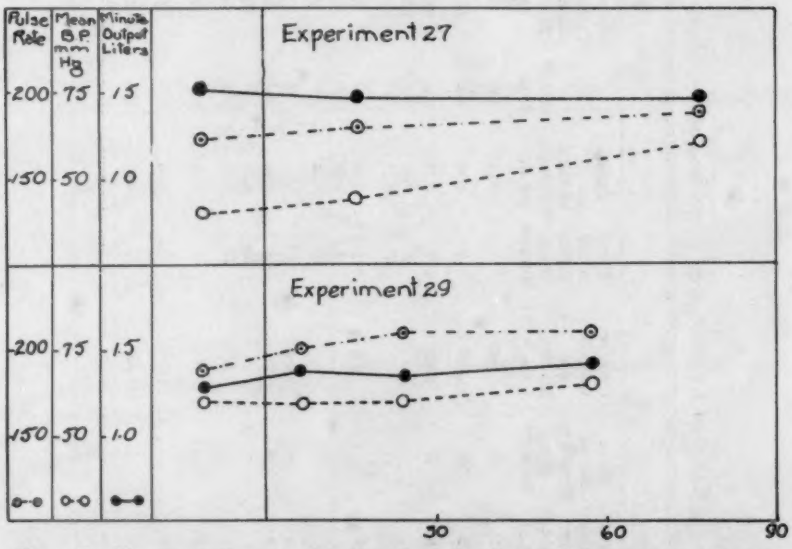

Chart 5.—Two experiments showing that strychnine did not affect the circulation of dogs in a state of hemorrhagic shock.

should not be given in shock. Of the several therapeutic measures which have been applied in this study, digitalis has been the most consistently harmful and has uniformly been without benefit.

2. Strychnine. The results with this drug are shown in table 4 and chart 5.

No effect on the general condition of the animals was noted. The oxygen consumption was diminished in two instances and increased in seven observations. The pulse rate was diminished in one experiment and increased in the others. Significant alterations in mean blood pressure were not found. The minute cardiac output was decreased after the administration of strychnine in two experiments. In seven other observations, the minute cardiac output after strychnine was given was

TABLE 5.—*Effect of Injection of Ether on Circulation of Dogs in State of Shock Produced by Hemorrhage*

		Before Ether						After Ether						
Experiment	Weight, Kg.	Time After Bleeding, Minutes	Total Amount Bled, Cc. per Kg.	Pulse Rate	Oxygen Consumption per Minute, Cc.	Mean Blood Pressure, Mm. Mercury	Cardiac Output per Minute, Cc.	Time After Giving Drug, Minutes	Total Amount of Drug Given, Cc. per Kg.	Pulse Rate	Oxygen Consumption per Minute, Cc.	Mean Blood Pressure, Mm. Mercury	Cardiac Output per Minute, Cc.	Method of Administration
31	14	35	22	190	79.2	70	730	5	0.17	190	61.2	96	1,460	Intra-arterial
32	16	20	45	180	124.2	100	1,240	5	0.18	180	241.2	105	1,930	Intra-arterial
33	14	210	27	200	118.8	47	1,570	2	0.14	205	122.4	66	1,460	Intra-arterial
								10	0.14	210	122.4	71	1,330	
								22	0.14	210	104.4	63	1,110	
34	9	20	38	180	60.8	...	550	2	0.22	180	64.6	...	710	Intra-arterial
								7	0.22	190	49.4	...	430	
								18	0.22	200	51.3	...	410	
35	13	5	52	180	114.0	77	990	..	....	...	.....	...	.....	Intra-arterial
		40	52	190	112.0	50	770	4	0.15	190	66.5	115	660	
								10	0.15	200	53.2	107	400	
								22	0.15	200	45.6	23	260	
36*	13	135	35	200	82.8	50	760	3	0.15	200	99.0	54	800	Intramuscular
37	14.8	40	27	160	100.8	...	1,150	6	0.23	175	102.6	...	1,260	Intramusculor
38	15	60	20	185	131.0	...	1,020	8	0.20	185	135.0	...	1,110	Intramuscular

* Trained unnarcotized dog.

within 10 per cent of the value before. These results are contrary to the observations on normal dogs of Wilson, Harrison and Pilcher,[13] who found that strychnine produced increased minute output. The discrepancy between their results and those obtained in this study indicates that the action of the drug on normal animals is different from the effect on animals in a state of shock. In the latter, strychnine is either useless or harmful.

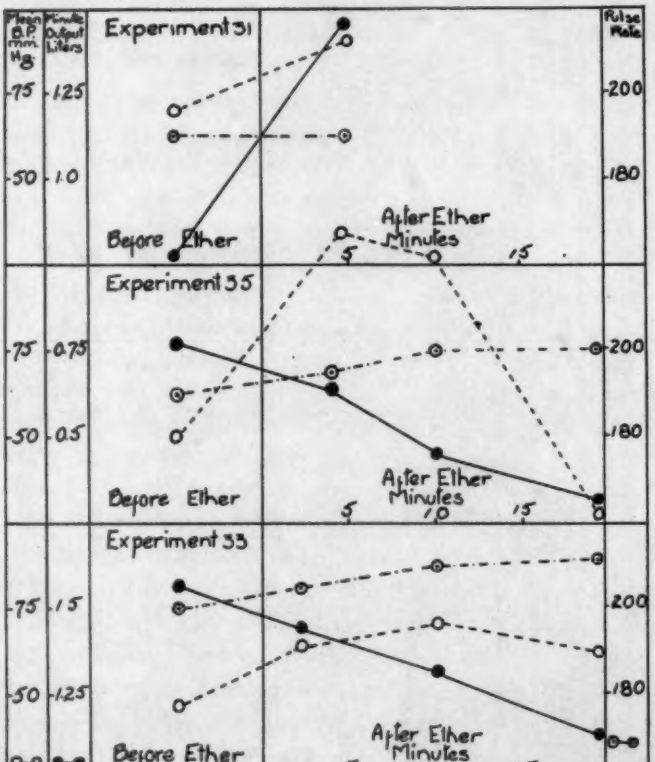

Chart 6.—Effects of injection of ether on circulation of dogs in a state of hemorrhagic shock. The variability of the drug is shown. In each instance there was a temporary rise in blood pressure, but the cardiac output was markedly increased in one experiment and greatly diminished in two others.

3. Ether. In the use of this drug marked variability characterized the results, which are exhibited in table 5 and chart 6. When administered intramuscularly, ether did not cause any significant change in pulse rate or blood pressure and slight (less than 10 per cent) increase in minute cardiac output. When administered intravenously, ether caused the immediate death of the animal. After intra-arterial injections the

13. Wilson, C. P.; Harrison, T. R., and Pilcher, C. P.: To be published.

TABLE 6.—*Effect of Caffeine on Circulation of Dogs in State of Shock Produced by Hemorrhage*

		Before Caffeine						After Caffeine						
Experiment	Weight, Kg.	Time After Bleeding, Minutes	Total Amount Bled, Cc. per Kg.	Pulse Rate	Oxygen Consumption per Minute, Cc.	Mean Blood Pressure, Mm. Mercury	Cardiac Output per Minute, Cc.	Time After Giving Drug, Minutes	Total Amount of Drug Given, Mg. per Kg.	Pulse Rate	Oxygen Consumption per Minute, Cc.	Mean Blood Pressure, Mm. Mercury	Cardiac Output per Minute, Cc.	Method of Administration
40	7.6	55	50	210	72.7	...	750	12	16	210	72.7	...	820	Intravenous
41*	7	40	34	150	73.8	...	720	7	17	150	97.2	...	1,010	Intravenous
42	7.2	60	38	130	63.0	...	630	20	25	150	73.1	...	750	Intravenous
								5	93	180	71.6	...	770	
								40	93	200	72.0	...	580	
43	5	25	32	170	41.4	...	530	12	22	120	57.6	...	700	Intravenous
		25	14	190	54.0	...	520	5	44	190	50.4	...	470	
								23	44	195	39.6	...	350	
44*	14	20	36	180	112.5	58	1,220	..	..	...	.....	...	.....	Intravenous
		33	36	180	117.0	56	1,110	3	4	180	108.0	82	1,700	
								7	4	180	115.2	80	1,480	
								18	4	180	117.0	80	1,390	
								40	4	190	97.2	40	930	
								75	4	190	117.0	52	1,100	
45	13.2	13	40	180	61.9	56	940	..	..	...	.....	...	.....	Subcutaneous
		25	40	180	61.9	56	820	20	15	180	72.8	54	960	
								45	15	180	80.1	51	1,010	
46	10.9	10	20	192	100.2	76	1,240	20	15	200	105.4	79	1,170	Subcutaneous
								42	15	192	92.5	73	920	
47	14	35	25	170	109.8	70	1,080	7	9	180	118.8	76	1,170	Subcutaneous

* Trained unnarcotized dog.

pulse rate was unchanged or slightly increased, and the mean blood pressure was elevated. The minute cardiac output was strikingly elevated (100 per cent and plus 57 per cent) in two experiments. When beneficial effects on the cardiac output and blood pressure were obtained, they came on within two minutes and were often followed within twenty minutes by depression. The observations on ether are in accord with the results previously published (Blalock [4]) concerning the effect of ether anesthesia on cardiac output. Increased minute output was found to occur during the early and usual stages of anesthesia, but prolonged ether narcosis caused a diminution in minute output.

4. Caffeine. The results with this drug are shown in table 6 and chart 7. In most of the experiments, the results were beneficial. The consumption of oxygen was often increased. The pulse rate was usually not altered. The mean blood pressure was increased in three observations, diminished once and unchanged in six instances, after administration of the drug. Of eighteen determinations after caffeine was given, the minute cardiac output was increased in nine, unchanged in six and diminished in three. Beneficial effects, when obtained, persisted for from thirty to sixty minutes. Harmful effects—diminution in minute output or mean pressure—occurred most often in those animals which were in a state of severe shock. In two experiments animals in severe shock died within a few minutes after being given caffeine. It was impossible to be certain whether the drug was the cause of death, although this seemed to be the case.

The results with caffeine, like those with strychnine, are contrary to the observations of Pilcher, Wilson and Harrison [14] on normal dogs. These observers found that caffeine caused either no change or diminution in minute cardiac output. In this instance also, the drug affects the normal and abnormal circulation in opposite directions.

5. Epinephrine hydrochloride. The results, which are exhibited in table 7 and chart 8, were not constant. The pulse rate was diminished significantly in one experiment only, and usually was not altered. The mean blood pressure was increased immediately after the intravenous administration of epinephrine hydrochloride, but it usually fell within a few minutes to below the level reached before the drug was given. Subcutaneous doses of epinephrine hydrochloride did not cause a significant rise of pressure. The minute cardiac output was diminished in one experiment and increased in three instances after the intravenous administration of epinephrine hydrochloride. The rise was poorly sustained, and the minute output within ten or fifteen minutes after the administration was less than that before the drug was given. The subcutaneous administration of epinephrine hydrochloride caused a rise

14. Pilcher, C.; Wilson, C. P., and Harrison, T. R.: To be published.

TABLE 7.—*Effect of Injection of Epinephrine Hydrochloride on Circulation of Dogs in State of Shock Produced by Hemorrhage*

		Before Ephinephrine Hydrochloride						After Ephinephrine Hydrochloride						
Experiment	Weight, Kg.	Time After Bleeding, Minutes	Total Amount Bled, Cc. per Kg.	Pulse Rate	Oxygen Consumption per Minute, Cc.	Mean Blood Pressure, Mm. Mercury	Cardiac Output per Minute, Cc.	Time After Giving Drug, Minutes	Total Amount of Drug Given, Mg. per Kg.	Pulse Rate	Oxygen Consumption per Minute, Cc.	Mean Blood Pressure, Mm. Mercury	Cardiac Output per Minute, Cc.	Method of Administration
50*	13	25	46	150	102.6	40	860	3	0.08	150	91.8	100	620	Intravenous
51	7.4	120	32	180	68.4	66	880	2	0.07	180	68.4	110	1,250	Intravenous
52	12.5	15	37	185	81.7	60	630	2	0.17	100	22.8	114	1,000	Intravenous
								6	0.17	120	43.7	88	2,140	
53	20	20	38	185	122.4	47	1,070	1	0.05	185	118.8	94	1,350	Intravenous
								5	0.05	185	137.0	34	1,220	
								10	0.05	185	108.0	34	920	
54	11	60	22	200	129.2	92	1,200	4	0.18	200+	129.2	90	1,300	Subcutaneous
								11	0.18	200+	125.4	56	1,200	
								30	0.18	200+	121.6	34	1,010	
55	13	45	30	90	102.6	80	1,470	7	0.15	120	137.8	90	2,090	Subcutaneous
								23	0.15	150	137.8	80	2,250	
								45	0.15	170	137.8	90	2,010	
56	13	50	29	215	66.6	50	550	5	0.08	215	63.0	40	490	Subcutaneous
								21	0.08	210	66.6	36	600	
								56	0.08	210	48.6	35	450	

* Trained unnarcotized dog.

in minute output. This came within from five to ten minutes and lasted from twenty to forty-five minutes. When the degree of shock was not extreme, the benefit derived from epinephrine hydrochloride was of longer duration than in those experiments in which the animal was in a more critical condition.

These results are in accord with the observations of Odaira [15] on normal rabbits; of Pilcher, Wilson and Harrison [16] on normal dogs, and of Lyon and Sands [17] on human subjects.

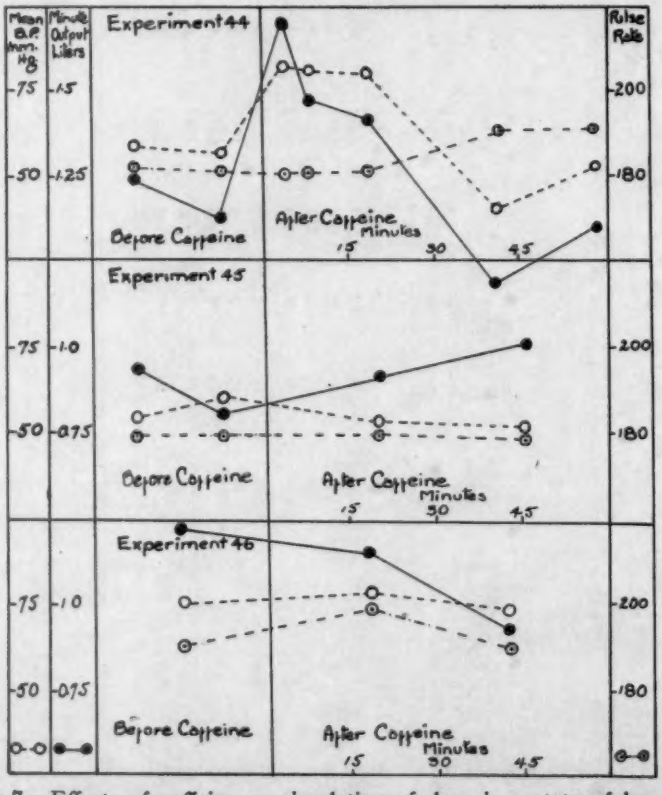

Chart 7.—Effects of caffeine on circulation of dogs in a state of hemorrhagic shock. In one experiment it was beneficial, as shown by the increase in both minute output and blood pressure. In the second and third experiments, the drug had little effect. Harmful actions were not usually observed after caffeine.

6. Ephedrine. The results with this substance were on the whole more satisfactory than those with any of the other drugs investigated.

15. Odaira, T.: Observations on Gaseous Metabolism and Minute Volume: I. Relation to Internal Secretions, Tohoku J. Exper. Med. **6**:325, 1925.

16. Pilcher, C.; Wilson, C. P., and Harrison, T. R.: To be published.

17. Lyon, D. M., and Sands, J.: Studies on Pulse Wave Velocity; Effect of Adrenalin, Am. J. Physiol. **71**:534, 1925.

TABLE 8.—*Effect of Injection of Ephedrine on Circulation of Dogs in State of Shock Produced by Hemorrhage*

		Before Ephedrine						After Ephedrine						
Experiment	Weight, Kg.	Time After Bleeding, Minutes	Total Amount Bled, Cc. per Kg.	Pulse Rate	Oxygen Consumption per Minute, Cc.	Mean Blood Pressure, Mm. Mercury	Cardiac Output per Minute, Cc.	Time After Giving Drug, Minutes	Total Amount of Drug Given, Mg. per Kg.	Pulse Rate	Oxygen Consumption per Minute, Cc.	Mean Blood Pressure, Mm. Mercury	Cardiac Output per Minute, Cc.	Method of Administration
57	13.2	30	27	176	95.7	77	1,420	..	..	...	.....	...	.....	Subcutaneous
		60	27	200	109.9	77	1,630	20	2	230	146.2	80	2,260	
								40	2	230	142.7	85	1,860	
								65	2	236	156.6	88	2,000	
								120	2	240	149.6	81	2,150	
58	16	25	40	230	129.6	69	1,130	15	2	180	147.6	66	1,230	Subcutaneous
								33	2	240	154.8	59	1,220	
								30	4	196	220.2	44	1,460	
								60	4	250+	179.2	44	1,160	
59*	11	123	20	192	92.5	73	920	20	2	168	114.7	79	1,120	Subcutaneous
								44	2	220	109.1	52	1.140	

* Trained unnarcotized dog.

They are shown in table 8 and chart 9. The consumption of oxygen was increased. The general condition of the animals seemed to be improved. The effects on pulse rate were inconstant. The mean blood pressure was slightly increased in five instances, slightly diminished twice, and markedly diminished in three observations after the administration of the drug. The minute cardiac output increased each time after the drug was given, and this rise was well sustained, lasting for

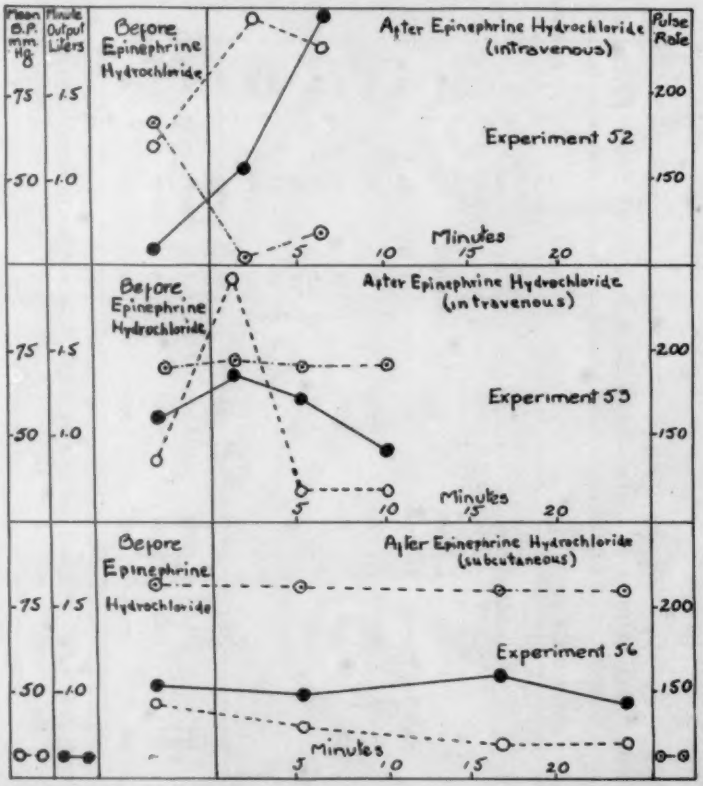

Chart 8.—Effects of epinephrine hydrochloride on circulation of dogs in a state of hemorrhagic shock. It was very beneficial in one instance, slightly beneficial in a second and without effect in the third experiment. In experiment 52 the effect of the drug was not studied after the first ten minutes. The short duration of the beneficial effects in experiment 53 should be noted.

from one to two hours. When the shock state was not extreme the animal seemed to be greatly benefited. There was less benefit when the animal was in severe shock. In two instances, moribund animals were given the drug. Both died before observations on the circulation could be made, and the impression was gained that the drug hastened their death.

TABLE 9.—*Effect of Intravenous Saline Infusion on Circulation of Dogs in State of Shock Produced by Hemorrhage* *

		Before Saline						After Saline					
Experiment	Weight, Kg.	Time After Bleeding, Minutes	Total Amount Bled, Cc. per Kg.	Pulse Rate	Oxygen Consumption per Minute, Cc.	Mean Blood Pressure, Mm. Mercury	Cardiac Output per Minute, Cc.	Time After Saline, Minutes	Total Amount Saline, Cc. per Kg.	Pulse Rate	Oxygen Consumption per Minute, Cc.	Mean Blood Pressure, Mm. Mercury	Cardiac Output per Minute, Cc.
61	15.3	70	20	200	108.2	70	830	4	13	180	131.4	78	2,610
62	18.3	88	31	195	180.0	78	1,600	15	17	160	169.2	74	1,910
63	9.5	80	33	200	87.4	55	750	14	13	200	87.4	70	1,190
								6	21	205	85.5	70	1,360
								25	21	205	83.6	71	1,070
								35	50	210	87.4	80	1,580
								285	50	190	85.5	77	1,270
64	14	40	32	185	122.4	90	980	60	21	180	124.2	110	1,150
65	13.6	150	22	170	118.8	84	1,040	7	12	100	144.0	78	1,820
66	14	35	25	170	109.8	70	1,080	5	14	150	135.0	105	1,540
67	11.4	24	43	150	86.4	79	910	4	18	150	124.2	95	2,410

* The animals received ether in experiments 64 and 65 and caffeine in experiments 66 and 67, in addition to saline infusion.

The results with ephedrine are in general accord with those obtained by Chen,[18] who used different methods on dogs in shock. He found that the increased blood pressure was due to increased cardiac output and not to arterial constriction. When his animals were in a severe state of shock, the drug was of little or no value, but Chen did not observe any harmful effects. In the present study the impression was gained that ephedrine might hasten death in animals already about to die. In no other instances were harmful effects seen.

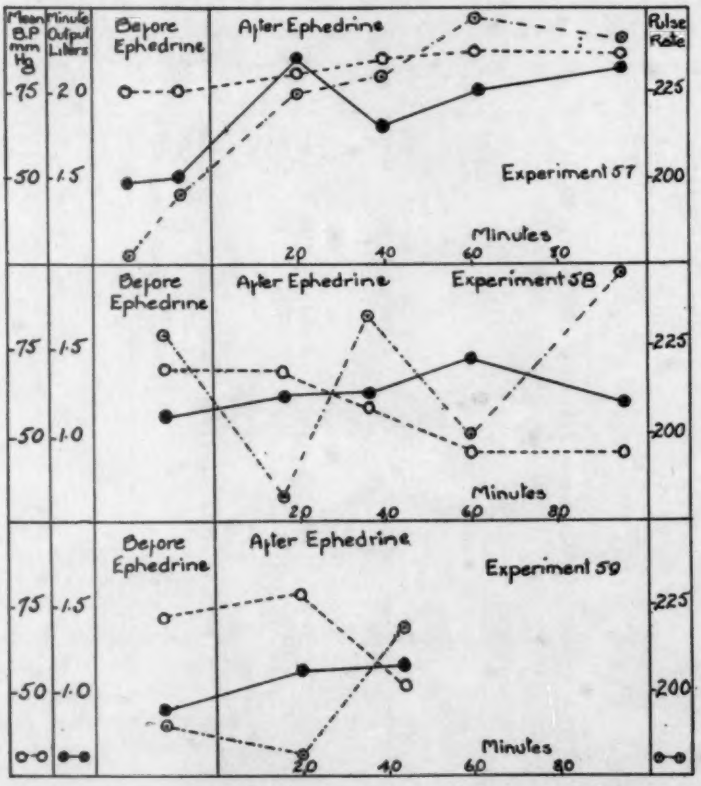

Chart 9.—Effects of ephedrine on circulation of dogs in a state of hemorrhagic shock. The minute cardiac output is increased in each instance, but the degree of increase is variable. The effects on blood pressure and pulse rate are less constant.

Chen used the myocardiographic method. Wilson, Pilcher and Harrison,[19] using the Fick method, observed increased minute cardiac output after giving ephedrine to normal trained unnarcotized dogs, and my results indicate that the action of the drug is similar in dogs in shock.

18. Chen, K. K.: Effect of Ephedrin in Experimental Shock and Hemorrhage, J. Pharmacol. & Exper. Therap. **26**:83, 1925.

19. Wilson, C. P.; Pilcher, C., and Harrison, T. R.: To be published.

TABLE 10.—*Effects of Hemorrhage on Maximum, Minimum and Mean Blood Pressure and Cardiac Output*

		Before Bleeding						After Bleeding							
Experiment	Weight, Kg.	Pulse Rate	Oxygen Consumption per Minute, Cc.	Maximum Blood Pressure, Mm. Mercury	Minimum Blood Pressure, Mm. Mercury	Mean Blood Pressure, Mm. Mercury	Cardiac Output per Minute, Cc.	Pulse Rate	Oxygen Consumption per Minute, Cc.	Maximum Blood Pressure, Mm. Mercury	Minimum Blood Pressure, Mm. Mercury	Mean Blood Pressure, Mm. Mercury	Cardiac Output per Minute, Cc.	Time After Last Bleeding, Minutes	Total Amount Bled, Cc. per Kg.
70	14.1	72	89	130	79	109	1,380								
		132	100	128	73	99	1,330								
		132	107	119	74	94	1,260	144	103	128	87	106	940	3	7
								220	98	108	76	90	680	25	12
71	12	52	78	160	54	95	1,860								
		60	74	166	53	94	1,600								
		90	69	172	53	101	1,570	56	75	144	75	105	1,640	15	10
								120	74	134	92	111	1,310	20	15
								200	87	130	97	114	1,020	20	20

As caffeine is probably more widely used clinically than any other drug in cases of shock, and since ephedrine seemed from this study to be the best of the various drugs studied, it was thought that a comparison of the action of these two substances might be of interest. The results of such an experiment performed on a trained unnarcotized animal are portrayed in chart 10. This dog had a normal minute cardiac output of 2,350 cc., and a normal mean blood pressure of 119 mm. of mercury. After repeated bleedings, the minute cardiac output was 1,240 cc., and the mean pressure was 76. Caffeine was given subcutaneously. Twenty minutes after the drug was administered the output was 1,170 cc. and the pressure 79. Forty minutes after caffeine was given the output was

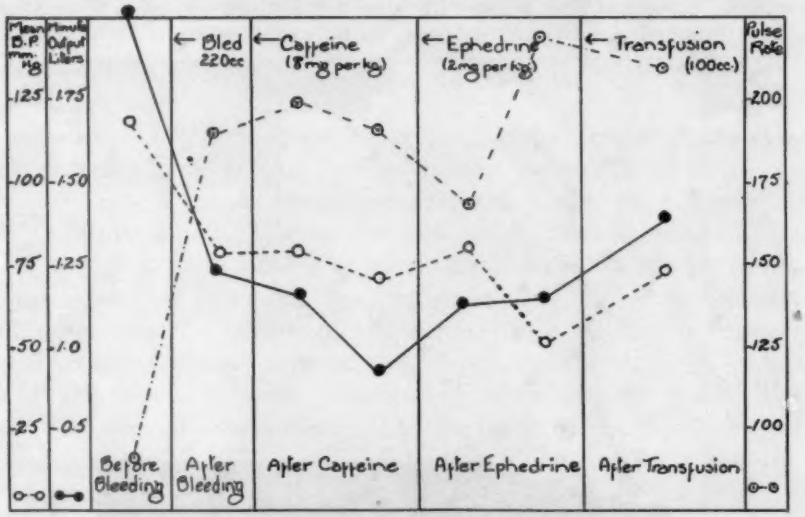

Chart 10.—Comparison of effects of caffeine, ephedrine and transfusion on circulation of a dog in a state of hemorrhagic shock. In this experiment the minute output and blood pressure continued to diminish after the administration of caffeine. Ephedrine caused a lasting increase in minute output and a temporary increase in blood pressure. Transfusion had the usual effect (chart 4).

920 cc. and the pressure 73. Ephedrine was administered. The pulse rate, which had not been altered by caffeine, decreased from 192 to 168. Twenty minutes after the administration of ephedrine the minute cardiac output had increased from 920 to 1,120 cc. Forty-five minutes after the drug was given the minute output was 1,140 cc. The mean blood pressure rose 6 mm., and then dropped 20 mm. One hour after ephedrine had been given, transfusion of 100 cc. of blood was performed. Twenty minutes after transfusion the mean pressure had increased by 20 mm., and the minute cardiac output had increased from 1,140, to 1,400 cc. However, one hour after transfusion the minute

cardiac output had fallen to 800 cc., and the blood pressure to 48, the lowest level yet attained. Shortly after this, the dog died.

This animal was in a state of severe shock before any therapeutic measures were instituted. Despite (or possibly because of) the administration of caffeine, the minute output decreased. Ephedrine caused temporary improvement. Transfusion caused further temporary improvement, but the degree of the original shock was too great for the animal to be saved. This experiment seemed to demonstrate clearly the superiority of ephedrine over caffeine.

Saline Infusion: The results are shown in table 9 and chart 11.

In every instance, the infusion of saline solution was followed by beneficial effects. The pulse rate was usually diminished. The mean

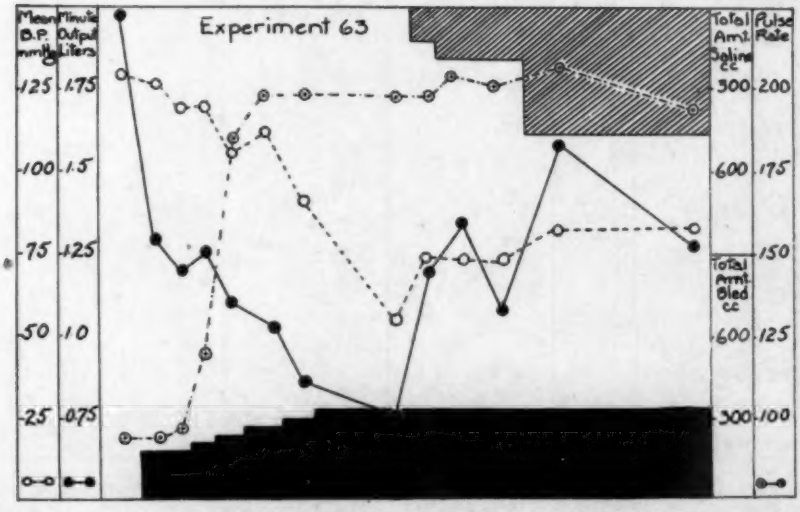

Chart 11.—Effects of bleeding and saline infusion on circulation. Progressive hemorrhage caused the minute cardiac output to decrease. The pulse rate then increased, and finally the mean blood pressure diminished. After the first saline infusion a striking rise in minute output and a small rise in blood pressure occurred. The tendency of the blood pressure rise to be sustained and of the minute output to decline again after saline infusion are illustrated.

blood pressure was slightly decreased twice, and was increased in the other nine observations after the administration of saline solution. The minute cardiac output was increased in every instance, and the immediate rise was as great or greater than that produced by transfusion. The immediate benefits of saline solution were comparable to those from transfusion, but the results were less lasting, the animal tending to relapse into a state of shock within from one to three hours. The temporary and permanent effects of saline infusion were much better than those of any of the drugs investigated.

COMMENT

It is not practical to separate hemorrhage and shock completely in any consideration of the mechanism of their production. The two are usually seen together clinically and are often observed concurrently in laboratory animals. The present report contains only experiments on hemorrhage, and the following comment is limited to this specific type of shock so far as such a limitation seems consistent with clearness.

All investigators are agreed that the symptoms of shock following hemorrhage are primarily dependent on a diminished volume of blood. So far as the immediate condition is concerned, the loss of hemoglobin is in itself relatively unimportant.

At this point agreement ends. Concerning why and how loss of blood volume causes such profound disturbances of body function, there is no unanimity of opinion. There have been at least three opposing schools:

1. *Venopressor Mechanism.*—Henderson and Harvey [20] showed that high carbon dioxide tension had little effect on arterial pressure, but caused a marked rise in venous pressure and, hence, they believed, in minute cardiac output. Conversely, low carbon dioxide tension caused a low venous pressure, which led to a diminution in the minute cardiac output and eventually to a low arterial pressure. According to this conception, carbon dioxide is to be regarded in the nature of a hormone which regulates venous pressure and, hence, indirectly affects cardiac output and arterial pressure. Low carbon dioxide tension was believed to be the result of overventilation and the cause of the circulatory collapse in shock.

A great many objections have been raised to this theory, and it is generally admitted to be no longer tenable. Overventilation and low carbon dioxide tension, when they occur, are now generally recognized as effects and not causes of shock.

2. *Diminished Arterial Pressure.*—The prognostic value of arterial pressure in severe shock is universally admitted. The question is: Does a fall in arterial pressure antedate and initiate the other circulatory changes in shock? Apparently most observers believe so. The blood pressure is widely used both clinically and experimentally as a "guide" to the degree of shock. Wiggers [21] recorded changes in arterial, intra-

20. Henderson, Y., and Harvey, S. C.: Shock and Acapnia; Veno-Pressor Mechanism, Am. J. Physiol. **46**:533, 1918.

21. Wiggers, C. J.: Shock: Abdominal—Initial and Progressive Stages of Circulatory Failure in Abdominal Shock, Am. J. Physiol. **45**:485, 1918; Shock and Circulatory Failure Following Trauma, ibid. **46**:314, 1918; Differentiation Between Circulatory Failure Due to Shock and Other Causes, J. A. M. A. **70**: 508 (Feb. 23) 1918.

ventricular and intra-auricular pressures by the optical method. He concluded that essentially the same circulatory mechanism prevailed in abdominal shock (exposure of intestines), traumatic shock and hemorrhage. In regard to the initial stages of abdominal shock,[22] he said: "As the contour of the intraventricular curves does not alter, as the heart rate, if it undergoes any change increases and as the pulmonary arterial pressure remains unaffected, the conclusion is reached that the reduction in blood content and fall in pressure in the arteries is not due to a decrease in the minute volume of the heart, but to a reduction in the total arterial resistance." Wiggers believed that the later and more significant fall in blood pressure was dependent on reduced minute cardiac output. Concerning hemorrhage, he wrote: "Reduction of arterial resistance initiates the fall of arterial pressure; . . . diminished venous return, a fall of effective venous pressure and a deficient cardiac discharge are prominent factors in the fatal fall of arterial pressure." Wiggers pointed out [23] that mean blood pressures might not adequately demonstrate the "distinct alteration" in "arterial pressure as recorded precisely." In my own experiments, mean blood pressure tracings have been used generally, and optical methods of registration have not been available. In order to meet Wigger's point, a few additional experiments have been done, and maximum and minimum pressures recorded. An example is shown in table 10.

These experiments show that the maximum pressure may fall and the minimum pressure may increase before there is a marked reduction in minute cardiac output. As the minimum pressure increases soon after bleeding, I cannot agree with Wiggers that the earliest changes in blood pressure are due to diminished peripheral resistance. The initial changes in blood pressure are to be considered as secondary to (1) compensatory vasoconstriction and (2) diminished output per beat. The minute output is usually diminished, but in those experiments in which tachycardia develops early the minute output may remain normal while the initial changes in blood pressure occur.

3. *Diminished Volume Flow of Blood.*—Gesell [24] studied the blood flow through the salivary gland and the mean arterial pressure. He compared the effects of hemorrhage and shock resulting from tissue-abuse. As my conclusions reached from a study of the total circulatory minute volume are strikingly similar to his, based on observations of blood flow through a small portion of the body, I quote Gesell as follows:

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22. Wiggers (footnote 21, first reference).

23. Wiggers (footnote 21, second reference).

24. Gesell, R.: Studies on the Submaxillary Gland: IV. A Comparison of the Effects of Hemorrhage and Tissue-Abuse in Relation to Secondary Shock, Am. J. Physiol. **47**:468, 1918.

Volume flow of blood appeared to be the more fundamental problem, and, as the results will show, mean blood pressure gives very little evidence of the gravity of the disturbance. A primary rise in pressure occurring both in hemorrhage and tissue-abuse may be accompanied by a large decrease in volume flow of blood, constituting the greater part of the total decrease reached by a subsequent fall to zero pressure. It appears that too much weight is still given to the mean blood pressure, relative to the conditions obtaining. Here lies a danger of permitting the development of shock which might otherwise be avoided . . . similarity of the curves resulting from hemorrhage and tissue-abuse. It appears, therefore, that fundamentally the same factors controlling volume flow of blood are operating in the two conditions. All the experiments indicate the similarity of the vascular reactions in hemorrhage and tissue-abuse . . . the percentage decrease in volume flow of blood far exceeds the percentage decrease in blood volume in every experiment. The maintenance of a normal blood volume is, therefore, an extremely important function.

A reduction of volume flow amounting to 85 per cent of the initial flow may occur with a constant head of pressure or with a small change in head of pressure—a rise as well as a fall.

Gesell emphasized the importance of the "nutrient flow," that is, the minute volume of flow multiplied by the percentage of red cells. He pointed out that the injection of an "inert" solution, although it caused a dilution of the blood and a diminished percentage of red blood cells was, nevertheless, of great benefit, because the degree of increase in volume following such injection was much greater than the degree of dilution. This he explained by Poiseuille's law concerning the rate of flow of liquids through tubes. This rate of flow, other factors remaining constant, increases with the fourth power of the caliber of the tubes, whereas the degree of dilution increases only with the square of the caliber:

The similarity of the curves of basal flow in hemorrhage and tissue-abuse suggests similar vascular reactions of similar origin, a change in caliber of the vessels being the most important factor underlying the deflection of the curves.

Aub and Cunningham,[1] using the Fick method, found that the cardiac output might diminish before the blood pressure reached a shock level. In their experiment 56, the mean blood pressure was between 104 and 94 mm. of mercury, whereas the oxygen content of the venous blood had fallen from 12.27 to 4.55 per cent by volume.

Cannon and Cattell,[25] in discussing the mechanism of shock, referred to Gesell's work and suggested that whereas the blood flow through the peripheral organs might be reduced before the blood pressure diminished, the blood flow through the vital organs might be normal until the fall in

25. Cannon, W. B., and Cattell, M.: Studies in Experimental Traumatic Shock—Critical Level in a Falling Blood Pressure, Arch. Surg. **4**:300 (March) 1922.

blood pressure occurred. However, Cannon [26] summarized the important physiologic abnormalities in shock and did not mention diminished minute cardiac output, which, from the work of Gesell, the studies of Aub and Cunningham and the results reported in this paper, seems to be the most important factor concerned, except the diminished blood volume.

My results are, in general, in rather close agreement with those of Gesell. He found somewhat greater reductions in volume in the flow of blood before the blood pressure began to diminish. It is to be expected, however, that the peripheral organs would show a relatively greater reduction in blood flow than would the total organism, for all compensatory mechanisms would act toward maintaining a normal or nearly normal flow in the more vital organs. This is in accord with the suggestion of Cannon and Cattell, previously mentioned.

The diminished oxygen consumption found in these experiments—also noted by Aub [27] and others—might conceivably be due to (1) a diminished oxygen requirement from impaired functional activity, or (2) an oxygen intake less than the oxygen requirement of the tissues due to the inability of the circulation to meet the demands of the body for oxygen. Hill and his collaborators [28] have distinguished between oxygen intake and oxygen requirement, and have shown that when the latter exceeds the former oxygen debt results. When an oxygen debt of any considerable magnitude occurs, lactic acid accumulates. The experiments of McLeod [29] indicated that the blood lactic acid is not significantly increased until shock becomes extreme.

The results of transfusion in my experiments indicate that both the factors mentioned previously may be effective in the diminished oxygen consumption during shock. The oxygen consumption after transfusion was usually greater than that immediately before this procedure. In some experiments it was less than the normal value for the animal and in some it was considerably greater than normal. In the former instances, that is, subnormal oxygen consumption after transfusion, it is logical to believe that the oxygen requirement during shock was diminished, whereas in the latter observations, that is, elevated oxygen consumption after transfusion, it seems evident that there was an actual oxygen debt during shock and that this was met by an increased oxygen consumption after transfusion.

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26. Cannon, W. B.: Studies in Experimental Traumatic Shock; Evidence of a Toxic Factor in Wound Shock, Arch. Surg. **4**:1 (Jan.) 1922.

27. Aub, J. C.: Studies in Experimental Traumatic Shock; Basal Metabolism, Am. J. Physiol. **54**:388, 1920.

28. Hill, A. V., and Tupton, H.: Muscular Exercise, Lactic Acid, and Supply and Utilization of Oxygen, Quart. J. Med. **16**:135, 1925.

29. McLeod, J. J. R.: Concentration of Lactic Acid in the Blood in Anoxemia and in Shock, Am. J. Physiol. **55**:184, 1921.

A great deal has been written about disturbances in acid base equilibrium in shock. At one time Henderson and Harvey [20] attributed the symptoms to acapnia (alkalosis from loss of carbon dioxide by overventilation), whereas Cannon [30] believed that acidosis was an important factor in shock (Cannon used acidosis to mean "diminished alkali reserve"). Wilson [31] found an initial fall in blood bicarbonate, followed by a rise above normal and an alkalosis in experimental hemorrhage. More recently, Hertzman and Gesell have reported increased alkalinity of the arterial blood and increased acidity of the venous blood after hemorrhage. They attributed the arterial alkalosis to overventilation and the venous acidosis to a diminished volume of flow.

The disturbances in acid base balance during hemorrhage and probably also during shock apparently may be explained on the basis of the changes in minute blood flow. They are, in all probability, to be attributed in large measure to anoxemia dependent on diminished blood flow and consequent low tissue oxygen tension. In moderate degrees of shock with relatively slight impairment of medullary circulation, mild anoxemia of the respiratory center would tend to produce overventilation and alkalosis. In extreme degrees of shock when oxygen intake fails to keep pace with oxygen requirement, oxygen debt occurs, lactic acid accumulates and acidosis results. Koehler, Brunquist and Loevenhart [32] have demonstrated that arterial anoxemia causes an initial alkalosis which is succeeded by acidosis if the anoxemia continues. There is no reason to assume that stagnant anoxemia has a different action from arterial anoxemia. In the long run, both exert similar effects on the tissues.

Thus, acapnia and acidosis are both to be regarded as characteristic of shock. They come at different degrees. Both are at least partially dependent on diminished blood flow, and neither is the cause of shock.

One other point is noteworthy in regard to the anoxemia. Harrison and Blalock [33] demonstrated that severe anoxemia increases minute cardiac output, and Harrison, Wilson, Neighbors and Pilcher [34] have demonstrated that mild anoxemia often has a similar effect. In shock, tissue anoxemia is present in marked degree. Despite this stimulus the minute cardiac output remains low because of the insufficient volume

30. Cannon, W. B.: Acidosis in Cases of Shock, Hemorrhage and Gas Infection, J. A. M. A. **70**:531 (Feb. 23) 1918.

31. Wilson, D. W.: Neutrality Regulations in the Body, Physiol. Rev. **3**:293, 1923.

32. Koehler, A. E.; Brunquist, E., and Loevenhart, A.: The Cause of Death in Anoxemia, J. Biol. Chem. **64**:313, 1925.

33. Harrison, T. R., and Blalock, A.: The Regulation of Circulation: VI. The Effects of Severe Anoxemia on the Cardiac Output of Dogs, Am. J. Physiol. **80**:169, 1927.

34. Harrison, T. R.; Wilson, C. P.; Neighbors, D., and Pilcher, C.: To be published.

of the blood. As anoxemia is a more constant and stronger stimulant to the circulation in normal animals than any drug which has been studied, it is not to be expected than any drug can do—in striking degree—what the natural stimulus fails to do. From this point of view, the beneficial action of ephedrine is rather surprising. The diminished cardiac output, despite tissue anoxemia, constitutes another reason for saying that the primary object of treatment should be to restore the

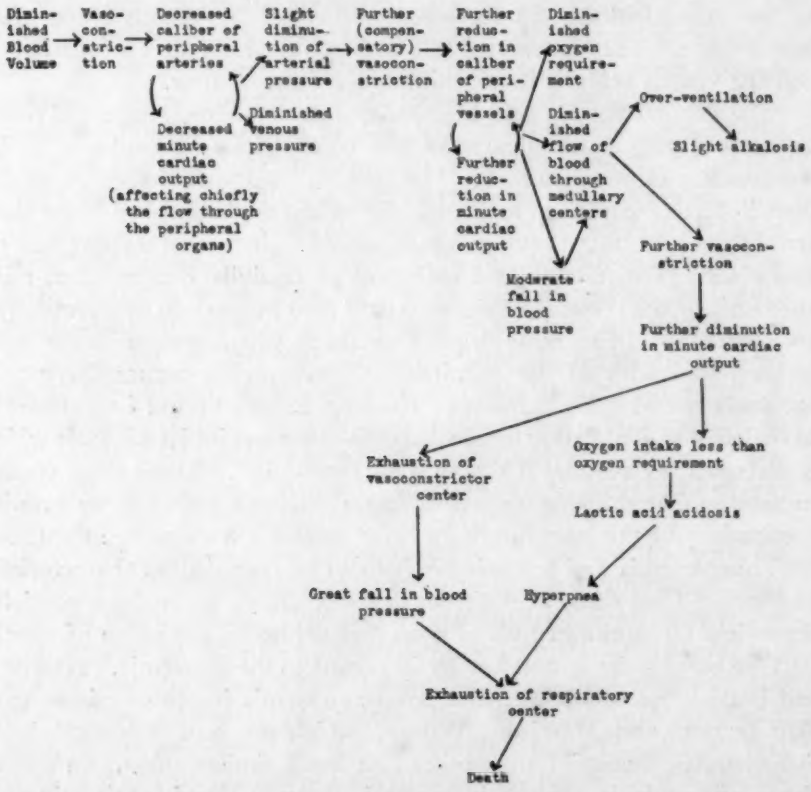
Diminished Blood Volume
Vasoconstriction
Decreased caliber of peripheral arteries
Slight diminution of arterial pressure
Further (compensatory) vasoconstriction
Further reduction in caliber of peripheral vessels
Diminished oxygen requirement
Diminished venous pressure
Decreased minute cardiac output (affecting chiefly the flow through the peripheral organs)
Diminished flow of blood through medullary centers
Over-ventilation
Slight alkalosis
Further reduction in minute cardiac output
Moderate fall in blood pressure
Further vasoconstriction
Further diminution in minute cardiac output
Exhaustion of vasoconstrictor center
Oxygen intake less than oxygen requirement
Lactic acid acidosis
Great fall in blood pressure
Hyperpnea
Exhaustion of respiratory center
Death

Chart 12.—Successive steps in the mechanism of shock resulting from hemorrhage.

volume of the blood. When this is done, the circulation responds to the stimulus of anoxemia, which is thereby diminished in degree.

The successive steps in the mechanism of shock resulting from hemorrhage would seem to be approximately as shown in chart 12.

Gesell's studies, as well as those of Wiggers, indicated an essential similarity between shock and hemorrhage so far as their effects on the circulation were concerned. My own observations on other types of shock than that following hemorrhage are far from completed, but they seem to indicate the same general relationship between mean blood pres-

sure and minute cardiac output as have been reported in this study. It appears, therefore, that the circulatory reactions in both hemorrhage and shock are results of a diminished circulating blood volume, initiated in the one case by loss of blood from the body and in the other by capillary dilatation—from histamine-like poisons, splanchnic vasodilatation or other causes—causing loss of circulating blood into the body. This conception is now generally accepted, and is in no sense original with me.

It is believed that the observations reported in this study are not without clinical significance, and some of the more important points in this connection will now be mentioned.

These experiments are more nearly comparable to clinical conditions than those previously reported, because the animals were not subjected to any operative procedure other than the insertion of an arterial cannula, and also because in several of the experiments no narcotic was used.

The results indicate quite definitely that no single factor of the blood pressure is of paramount value as a guide to incipient shock. The circulation has already become seriously impaired before significant changes in systolic blood pressure occur. The relationship existing between diastolic and systolic pressure or that existing between diastolic pressure and its previously known value are of significance. The pulse pressure and the pulse rate should be more satisfactory clinical guides, although, as has been pointed out, the pulse rate may remain normal after a notable decline in the minute cardiac output has occurred. The pulse rate always increases before the blood pressure diminishes and hence, of the two, is a better criterion of the onset of shock. Therapy should not be delayed until the blood pressure is definitely "below normal." A low level of blood pressure indicates a moribund patient, and even transfusion may be expected to fail often in such instances.

Any patient, who, after hemorrhage, has a significant tachycardia, should be treated for incipient shock.

In regard to the choice of therapeutic measures, the results of this study emphasize the relative uselessness of drugs as contrasted to the procedures which restore the volume of blood. These results are in accord with general clinical experience.

Digitalis is used frequently in treatment for shock. Because the drug is of great value in most types of circulatory failures due to cardiac disease, there seems to be a general impression that circulatory failure from any cause constitutes an indication for digitalis. The administration of digitalis preparations in shock cannot be too strongly condemned. Of all the therapeutic measures studied, digitalis was the most universally harmful. This conclusion is in accord with that drawn by Harrison and Leonard from their study of this drug in normal animals. I agree with their statements in reference to digitalis in shock:

The evidence presented suggests that when so used the drug may be harmful. As a matter of fact when digitalis is given to these patients it is often administered intramuscularly as digifolin in doses of one to three cubic centimeters a day, and such doses probably have no effect at all. If the drug were administered in full amount in such cases we should probably see harmful effects occasionally. As it is one does not usually observe any effect from digitalis in these patients.

Ether may be beneficial, but in some instances it is harmful. The same may be said of epinephrine hydrochloride. Both of these substances have too evanescent an action to be of any lasting value, and the immediate stimulation following their administration may be followed by depression. Epinephrine hydrochloride should never be given intravenously in shock, as the beneficial action lasts only a few minutes. The best results from ether were obtained by intra-arterial administration, a method which is impractical in the clinic, and dangerous, in any event.

Caffeine appears to do some good in mild shock. The optimum dose appears to be from 0.25 to 0.5 Gm. of the pure drug, or twice this amount of caffeine sodium benzoate for a patient of average size. Too much faith should not be placed in caffeine. It may be without value in moderate degrees of shock and is certainly without value in severe shock.

Ephedrine appears to be the best of the drugs. In animals moribund from extreme shock it appears sometimes to be harmful, but such instances are hopeless no matter what form of therapy is used. The effects of various doses of ephedrine have not been determined in this study. The beneficial effects in the animals followed doses of 2 mg. per kilogram (approximately 0.13 Gm., or 2 grains, for a patient weighing 140 pounds [63.5 Kg.]).

The value of saline infusion and transfusion in hemorrhage has been proved clinically. These experiments indicate that they should be employed early, before the blood pressure falls, and in abundant amounts.

The following procedures are suggested as a tentative routine treatment of any hemorrhage of significant magnitude. (Hemorrhage of more than 1 liter may probably be regarded as "significant" from this point of view.)

1. As soon as the patient is seen and the hemorrhage is controlled, he should be given from 65 to 130 mg. (1 to 2 grains) of ephedrine subcutaneously.

2. Intravenous saline infusion should be instituted as soon as possible, and relatively large amounts should be given. Ordinarily, one need not have any fear of "embarrassing the heart." Provided there is no structural cardiac disease and no pre-existing hypertension of severe degree, and the patient is under 60 years of age, the heart will be able to take care of any reasonable amount of fluid added to the circulation. During the first hour 1 liter of saline solution should be given into the

vein. Thereafter, subcutaneous infusion should be employed until transfusion can be carried out.

3. As soon as the saline infusion has been begun, the preliminary measures (procuring a donor and matching the blood) for transfusion should be instituted. If the patient's condition appears relieved, transfusion may not be necessary. If marked tachycardia persists, and more particularly if the systolic blood pressure is below 100 to 110, the transfusion should be performed.

4. If, after the conclusion of transfusion, the patient's condition remains precarious, the whole process should be repeated.

It is admitted that by this routine plan of treatment a great many unnecessary transfusions will be done. It is believed, however, that severe shock will sometimes be prevented and a life which otherwise would be lost will occasionally be saved.

When the hemorrhage is from an internal organ and necessitates an operation, general anesthesia should not be used. The present work indicates that ether is dangerous. Previous work suggests that chloroform, which decreases minute cardiac output, and ethyl chloride, which often has the same effect (Blalock[5]), would probably be distinctly harmful. Clinical experience and experimental results agree in indicating that local anesthesia should be employed for operations on patients who have bled profusely.

SUMMARY AND CONCLUSIONS

The pulse rate, consumption of oxygen, mean blood pressure and minute cardiac output have been studied before and after successive bleedings in morphinized dogs and in trained unnarcotized dogs. In a few experiments, maximum and minimum arterial pressures were recorded. The methods which were used did not require any operative procedure except the insertion of an arterial cannula and cardiac punctures. Repeated hemorrhages cause a diminution in minute cardiac output, which usually precedes the increase in pulse rate and always precedes any significant fall in mean blood pressure. The minute cardiac output is usually from 30 to 50 per cent below the normal level before a marked diminution in mean blood pressure occurs.

These observations are interpreted as meaning that the essential circulatory effects of a diminished volume of blood are (1) decreased minute cardiac output and (2) diminished caliber of peripheral arteries. It is believed that the other circulatory effects are secondary. The blood pressure is an inadequate guide to the state of the circulation in incipient shock.

Various therapeutic measures have been instituted and their effects studied. In general, it may be said that drugs are relatively useless as

compared to those measures which tend to restore blood volume. Transfusion of blood and intravenous saline infusion are beneficial, but they may fail in animals which have been in a severe state of shock for a considerable period. The effects of drugs may be summarized as follows: 1. Digitalis is always harmful. 2. Strychnine is usually useless. 3. Epinephrine hydrochloride and ether have uncertain actions, and their effects are too evanescent to be of lasting value in most instances. 4. Caffeine is slightly beneficial when the shock is not severe. 5. Ephedrine seems to be better than any of the drugs studied. It is more beneficial than caffeine, but much less so than the administration of fluid or blood.

On the basis of these observations certain physiologic considerations of shock are discussed, and a tentative routine treatment of severe hemorrhage is suggested.

A REVIEW OF UROLOGIC SURGERY

ALBERT J. SCHOLL, M.D.
LOS ANGELES
E. STARR JUDD, M.D.
ROCHESTER, MINN.
LINWOOD D. KEYSER, M.D.
ROANOKE, VA.
GORDON S. FOULDS, M.D.
TORONTO
JEAN VERBRUGGE, M.D.
ANTWERP, BELGIUM
AND
ADOLPH A. KUTZMANN, M.D.
LOS ANGELES

KIDNEY

Surgical Technic.—Chauvin [1] reported a case in which secondary nephrectomy was performed by means of thoracophrenolaparotomy. Several years previously the patient had been struck by a bullet, which had broken the tenth rib, perforated the pleural culdesac, and finally stopped in the right lobe of the liver. When the kidney was removed, it was found embedded in a thick, hard, fibrous mass. As sufficient exposure could not be obtained, even with resection of the twelfth rib, the pleural culdesac and the diaphragm were incised up to the ninth rib, which permitted ample operating space. Adhesions from an earlier empyema prevented pneumothorax.

Roseno [2] expressed the belief that pyelotomy is much superior to nephrotomy, if it can be performed. He stated that of 1,767 nephrotomies reported in twenty-five years 85 were secondary; 102 patients died, a mortality of 5.8 per cent. In contrast to this, in 950 pyelotomies reported in seventeen years, one of which was a secondary nephrectomy, seven deaths occurred, a mortality of 0.7 per cent. He attributed the more favorable results to the following reasons: (1) the opening is small and there is no cutting into the functioning parenchyma; (2) fistulas after pyelotomy are extremely rare; (3) the danger of operative and postoperative hemorrhage is slight, and (4) even in adherent kidneys, approach to the pelvis is always possible, especially

1. Chauvin, E.: Néphrectomie secondaire par thoraco-phréno-laparatomie, Press méd. **35**:250, 1927.

2. Roseno, Alfred: Die Nephrotomie Ihre Bedeutung und der Weg zur Verhütung ihrer Gefahren, Ztschr. f. Urol. Chir. **20**:96, 1926.

with Rosenstein's technic using the anterior wall of the pelvis. There are, however, several definite indications for nephrotomy:

1. Large stones that cannot be freed in any other manner, and stones that do not cast shadows or cannot be felt and are only demonstrated by splitting the kidney. Roseno reported such stones as occurring in from 1 to 4 per cent of cases in European clinics, while Braasch and Foulds found the following: In 146 cases, roentgenograms showed a single stone, but surgical exploration revealed more. In sixty-six cases roentgenogram showed multiple stones, and operation revealed but one. In twenty-one cases, roentgenogram did not show shadows, and operation showed one or more stones.
2. Early tuberculosis, exploratory nephrotomy.
3. Small tumors of the kidney, exploratory nephrotomy.
4. Congestion and bleeding from the capillaries of the papillae.
5. Injuries to the kidney.
6. Recurring renal colic on the basis of unilateral nephritis.
7. Suppurating renal infections associated with firmly embedded stones or stag-horn calculi.
8. Uremia due to nephritis or chronic obstruction.

In 1880, Morris was the first to cut into the kidney and extract a stone. In 1888, Von Czerny performed the first pyelotomy. The operations were described as simple, harmless and successful. At first, Israel and LeDentu advised packing only, but they soon introduced suturing the parenchyma after nephrotomy. This was kept up until 1908, when Zuckerkandl popularized pyelotomy. Since then the indications for nephrotomy have decreased because of danger of hemorrhage, fistula and marked destruction of parenchyma.

The classic method (Tuffier) is briefly described. The kidney is entirely freed and a tourniquet put around the pedicle. Incision is made from pole to pole. After removal of the stone, the parenchyma is sutured together. These sutures must be tight to check all bleeding and eliminate all dead space between the cut surfaces. Because of the softness of the parenchyma, the sutures often cut in; this was somewhat overcome by using mattress sutures.

Various attempts were made to improve the technic of nephrotomy, such as the Zondek incision; the Marwedel right angle incision; the blunt method of Rovsing and Hochenegg; the sawing technic of Cullen; plastic covering of the wound with muscle tissue, with fat and with connective tissue, and the tying of sutures over fat pads, care in preventing opening the pelvis (Heymann); the drainage method through the parenchyma to the outside or through the ureter into the bladder and the combination of drainage with ureteral catheter and nephropexy (Rehn). All these, however, have failed to eliminate the dangers of nephrotomy. The usual complications have been operative and postoperative bleeding and the formation of fistula. Every incision destroys blood vessels and parenchyma, which leads to infarction

followed by connective tissue organization and distortion of the normal adjacent parenchyma. The sutures also destroy the parenchyma by pressure atrophy. The problem has been to eliminate the use of sutures.

In the consideration of hemostasis, there are two types of bleeding in all wounds, parenchymal or oozing, and vascular. In the former there is danger if the patient is a "bleeder," or has a disease that may increase coagulation time, or if blood pressure is high as in arteriosclerosis. In both types it is difficult to secure thrombosis.

Often if blood vessels are cut they contract. Bleeding may not occur at the time, but later the vessels open and bleeding is profuse. This occasionally follows nephrotomy. Often the hemorrhage will continue until clots and coagulated blood are removed.

Three conditions are essential to prevent bleeding: (1) the formation of a clot should be prevented; (2) the nonactive blood vessels that may bleed later should be cared for, and (3) the cut surfaces should not be injured any more than is necessary.

Clinical observation shows three types of bleeding: (1) immediate at the time of operation, (2) shortly after operation and (3) from eight to fourteen days after operation. Bleeding in the wound leads to the splitting of sutures, and then bleeding into the perirenal tissues. Bleeding at operation from the large vessels is controlled immediately; this may be aided by Rovsing's incision or the multiple button-hole incisions of Magoun. The present treatment for postoperative hemorrhage is to pack and apply mattress sutures. Packing may cause bleeding when it is pulled out.

Roseno has suggested a change in technic. While there is no method of opening the kidney that will not tear blood vessels, he suggests that each vessel be carefully clamped and ligated. This puts the operation on an accurate and efficient hemostatic basis and leaves only slight oozing from the parenchyma which is of no consequence. He has applied this technic experimentally with good results. Both halves of the kidney will unite readily, there being no danger of later hemorrhage or the formation of a fistula; healing occurs with a minimum of scar formation. Anatomic studies have shown that there is no bridging of the scar by collateral circulation because all the vessels destroyed are terminal arteries.

From 1913 to 1925, 234 renal operations, of which 38 were nephrotomies, were performed in Roseno's clinic. Seven postoperative hemorrhages occurred; one stopped spontaneously; in two cases secondary operation was performed and the wound packed. The kidney was removed subsequently in one; in five secondary nephrectomy was performed; two patients died from the operation, and two patients died from urosepsis. The early work in this clinic was done by Israel

and Karewski; since Rosenstein has taken the service, all vessels in the wounds after nephrotomy have been ligated with better results.

Williamson [3] reported further work on transplantation of the kidney. He found that an autogenous transplant of the kidney will maintain the life of the experimental animal for several months after the removal of the other normal kidney. It was also found that during the time that the autogenous transplant is functioning, the urinary constituents are essentially normal and the animal behaves and lives normally. Because of contracture of the end of the ureter, however, hydronephrosis and infection supervene and cause the experiment to fail ultimately.

Homogenous and autogenous transplants function similarly, but only for a short period of several days except in rare instances. In these experiments in the animals with three functioning kidneys, two normal and one transplant, the blood urea was markedly reduced.

The site of the transplant does not materially lengthen the functional life or influence the terminal histologic picture, which is that of acute atypical glomerular nephritis followed by general acute nephritis. Infection as evidenced by the cytologic changes is not a factor in these experiments so long as good drainage and function are maintained. If the transplanted kidney is allowed to remain in place after aneuria develops there is a tendency for it to be replaced by fibrous tissue. The failure of homogenous transplants seems attributable to a biologic incompatibility between the donor and recipient. The value of the transplantation of the kidney as a clinical measure is questionable with our present knowledge, although under proper conditions it might be worthy of serious consideration.

Hinman and Morison,[4] in experiments on rabbits, ligated and divided the left ureter and then killed the animals in from seven to seventy days. Two were killed at one time; in one an arterial injection was combined with the injection of both ureters.

These studies showed that the arterial circulation of the rabbit's kidney is distributed in two planes within the parenchyma in relation to the renal pelvis. The main subdivisions of the renal artery pass around circumferentially, while the finer branches are distributed radially to the cavity of the pelvis. With the production of hydronephrosis, the arterial circulation undergoes two phases of alteration. The first phase, occurring at the onset, is relatively short and appears usually to be due to purely mechanical interference. The second phase which soon follows, in addition to the mechanical interference, has a reduction

3. Williamson, C. S.: Further Studies on the Transplantation of the Kidney, J. Urol. **16**:231, 1926.

4. Hinman, Frank, and Morison, D. M.: Experimental Hydronephrosis; Arterial Changes in the Progressive Hydronephrosis of Rabbits with Complete Ureteral Obstruction, Surg. Gynec. Obst. **42**:209, 1926.

in circulatory function causing atrophy and thereby accelerates the development of the hydronephrosis.

When ureteral obstruction occurs, the renal pelvis dilates and causes progressive compression of the enveloping parenchyma. Since the finer arterial branches traverse the parenchyma in a direction radial to the cavity of the pelvis, they are subjected early to compression in their long axes and consequently become tortuous and foreshortened. On continued obstruction, the kidney increases in circumference and therefore all structures in the circumferential course are either stretched or lengthened. Since the arteries are elastic tubes, they become attenuated and the lumina become smaller, with the resultant reduction in blood supply leading to ischemia, loss of tissue-tone and progressive atrophy.

Callahan and Schiltz [5] reported a case of aneurysm of the renal artery and reviewed the literature. About half of the cases reported are traumatic in origin; the remainder are spontaneous. Arteriosclerosis, syphilis, embolism, or some antecedent infection is usually the cause of the spontaneous type. Traumatic aneurysm is nearly always false, and spontaneous aneurysm is usually true.

The most important sequelae are: rupture into the pelvis, producing hematuria; rupture into the peritoneal cavity without consequent hematuria, and destruction of the kidney; the latter is characteristic of the false type; in comparison, true aneurysm causes little destruction of the renal substance.

Aneurysm of the renal artery causes abdominal pain which is closely followed by hematuria. The most valuable diagnostic sign is a palpable tumor in the region of the kidney. True aneurysm may persist for a long time without causing symptoms although hematuria, pain and tumor may occur. Practically all cases in which there are symptoms end fatally unless operation is performed, death occurring from two days to five years after onset. In the small true aneurysms the prognosis is much less serious, and in those which have become calcified, rupture is improbable.

Of the twelve patients operated on, ten were cured and two died. Nephrectomy was performed in ten cases. Orth was able to turn out the clots and successfully suture the tear, and in the authors' case it was also possible to excise the sac and preserve the artery. Orth reported good function a year later, and in the case reported by Callahan and Schiltz, function was still good six months following operation. In the authors' case a sacculated aneurysm was found in the renal artery; the sac was clamped, then ligated and excised. The perforated artery was closed without sacrificing the artery or any part of the kidney.

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5. Callahan, W. P., and Schiltz, F. H.: Aneurism of the Renal Artery, Surg. Gynec. Obst. **43**:724, 1926.

Dreyfuss,[6] after analyzing and reviewing the literature on pelvic kidney, stated that pathologically there are two types; the occasional pseudopelvic or movable kidney should be distinguished from the true pelvic kidney. The pelvic kidney is recognized more by the various symptoms within the pelvis than by differential diagnosis. Even the freedom from symptoms for many years is not against the appearance of any complaints of pelvic kidney, for in the course of time changes occur that may aggravate the condition. The diagnosis is made by the pyelogram which also demonstrates the presence of the other normally placed kidney. The function of the latter should always be demonstrated before operation. The presence of a normal kidney indicates the removal of the pelvic kidney, since much suffering may be averted. Nephropexy will take care of acquired pelvic kidneys and those types that lie between movable kidney and dystopia.

[ED. NOTE.—From a surgical point of view, the treatment in cases of ectopic kidney does not differ essentially from the treatment given when the organ is in its normal position. The mere fact that the kidney did not rise to its normal position does not indicate that treatment is required. If the kidney is functioning normally in its malposition, under ordinary circumstances it should not be disturbed. Usually it is difficult to change the position of the ectopic kidney because the blood vessels in the pedicle are short and the kidney is rather firmly fixed.]

Lipshutz and Hoffman[7] described a rather remarkable specimen showing in a composite form the important variations of the renal arteries and veins.

Variations in the renal arteries are perhaps more frequently met with than in other large arterial trunks, and the commonest variation is the presence of an additional renal artery. As many as five or six in one kidney have been reported. Abnormalities in form, position and development of the kidney in association with the accessory renal arteries may be noted. In general, the kidney deviates from its normal reniform shape in proportion to the number of vessels. In horseshoe kidneys additional renal vessels are the rule.

Organs that migrate far from their original position may retain vessels from this position or receive or incorporate vessels of the region invaded. The kidney, during its growth, migrates and undergoes rotation around its long axis. The instances of accessory renal arteries arising from the iliac arteries and from the middle sacral and inferior mesenteric arteries are to be considered as persisting embryonic vessels of the capillary plexus supplying the normal embryonic kidney.

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6. Dreyfuss, Wilhelm: Beitrag. zur Kenntnis der Beckenniere, Ztschr. f. Urol. Chir. **19**:277, 1926.

7. Lipshutz, Benjamin, and Hoffman, Clarence: Renal Arterial Variations and Extraperitoneal Abdominal Nephrectomy, Ann. Surg. **84**:525, 1926.

An accessory superior or inferior polar renal artery may originate from the renal artery proper and not from the aorta; Eisendrath directs especial attention to this variation. Some type of renal arterial variation is present in from 20 to 33 per cent of all subjects.

Undoubtedly insufficient attention is paid to the variations in the renal veins which are subject to a greater range of variations than are the arteries, and surgically are just as important.

Attention is called to the frequent production of hydronephrosis from compression of the ureteropelvic juncture by an accessory inferior polar renal artery.

An extraperitoneal abdominal approach for nephrectomy is described. The parietal peritoneum is stripped back carefully with elevation of the colon forward from the renal fossa. In this way the renal pedicle may be ligated primarily before the kidney is displaced, accessory vessels are dealt with, the danger of tear into the inferior vena cava is obviated, and congenital anomalies, such as horseshoe kidney and ectopia, can be better managed. The extraperitoneal abdominal route, according to these observers, finds more than rational application in the removal of large cysts and tumors of the kidney.

[ED. NOTE.—The problem of stripping back the parietal peritoneum, it would seem, usually has not been solved easily by surgeons. Many prefer the abdominal direct transperitoneal route for large tumors. Largely on theoretical grounds one would have to determine whether to use extraperitoneal or transperitoneal methods according to the size of the tumor, according to the ease with which the peritoneum strips away from the renal fossa and its adherence to tumor or inflammatory tissue.]

Renal Tumors.—Bothe [8] reviewed the conceptions of the genesis of hypernephroma which have been held by various pathologists and urologists from the time of Grawitz. The results of a survey of the voluminous literature show that the following theories have been propounded:

1. Hydronephromas originate in suprarenal cell-rests.
2. They are alveolar sarcomas having nothing to do with cell-rests.
3. They are endotheliomas that originate from the endothelial lining of perivascular lymph spaces.
4. They are classified, if benign, as adenoma, if malignant, as carcinoma.
5. They develop from the endothelial cells lining the blood vascular spaces.
6. They are derived from the epithelium lining the uriniferous tubules.
7. They originate from islands of embryonic nephrogenic tissue.

Bothe then considered the embryology of the suprarenal glands and the kidney, showing how these organs develop in juxtaposition and are intimately related in the relative position of their various anlagen.

8. Bothe, A. E.: Hypernephromata, Ann. Surg. **84**:57, 1926.

From a study of pig and human embryos in early stages, he showed that suprarenal rests may be encountered frequently in renal tissue, which may give rise to hypernephromatous neoplasia.

From chemical studies comparing the amount of ether-soluble material, cholesterol and lecithin in hypernephroma and suprarenal tissue, Bothe concluded that there is a striking similarity between the two. Likewise the injection of watery extracts of hypernephroma tissue into rabbits causes a rise in blood sugar and glycosuria, a feature suggestive of the relationship of hypernephromatous tissue to the cortex cells of the suprarenal gland.

The pathologic study of a series of nineteen cases from necropsy records at the University of Pennsylvania is tabulated. Three instances of hypernephroma in animals are cited.

Bothe showed that it is not uncommon for the neoplasm to grow into the lumen of the renal veins, as is well known, and also at times to invade the wall of the vein. Likewise the tumor may grow into the lumen of the ureter, but rarely invades the ureteral walls. While hypernephroma usually arises primarily in the kidney it is rarely found as a primary tumor in other organs such as the liver, falciform ligament, pelvis, uterus, suprarenal gland, tongue, ovary, broad ligament, spermatic cords, testis, retroperitoneal tissue, pancreas and ciliary body, instances of which are cited.

Metastatic hypernephroma is a reproduction in structure of the original tumor. The bones, lungs and liver are common sites. Metastasis may be an early feature of the disease and the growth in the kidney may be undemonstrable when the secondary growths may be prominent.

The tumor is prone to develop in the male. It usually occurs between the ages of 40 and 60 years.

In discussing pathology, Bothe showed that benign suprarenal rests are frequently found in renal tissue. They resemble, in histologic detail, the cells of the suprarenal gland. In a large microscopic section, he showed suprarenal rest tissue lying close to the proliferating hypernephromatous tissue, and considered that this indicated the possibility of hypernephromatous change in a suprarenal rest.

In general, Bothe concluded from his studies that from the embryologic, pathologic and chemical standpoints hypernephroma arises in a manner in accord with the views originally presented by Grawitz.

[Ed. Note.—Bothe's study is exhaustive and represents an excellent review of a moot subject. To just what degree he has demonstrated the correctness of his contention will be subject to dispute. While the evidence is not conclusive it does argue strongly for the suprarenal rest hypothesis which has suffered considerably during the last decade at the hands of various pathologists. It is difficult to anticipate just

what interpretation would be made of the author's large sections showing suprarenal rests and hypernephroma in the same section, by those who hold to the endothelial or renal-cell genesis. At any rate this article will not pass without considerable comment as it revives the grawitzian theory and will stimulate other studies leading to its support or refutation.]

Vercesi [9] described a case of a large primordial sarcoma of the kidney in a fetus. Histologically, he found that round and spindle-shaped cell types predominated. Vercesi believed that these cells belong to the hemogenous and lymphogenous endothelial variety. The tumor in this case was large enough to cause dystocia. The mother was found to have syphilis.

Marion [10] said that pyelography is of some help in the diagnosis of renal tumors, but that it should not be relied on entirely or regarded with too much importance, and that it is of little diagnostic value in hemorrhagic diseases of the kidney unless the kidney is enlarged. Pyelography that does not reveal a tumor may lull the examiner to a false sense of security, and thus a tumor, if present, increases in size; on the other hand, a blood clot in the renal pelvis may suggest tumor. Hematuria with blood clots not suggestive of tuberculosis, calculus, hydronephrosis or pyelonephritis is sufficient indication for a surgical examination of the kidney without consideration of the pyelographic picture. If, however, the kidney is large and there is no hematuria, it is necessary to resort to a pyelogram in order to determine whether or not the enlargement is the result of neoplasm.

Nicolas [11] noted that Israel has described many cases of hematuria with renal tumors, but that more rarely these cases show methemoglobinuria; such a case is reported in that of a man, aged 30, with tumor of the left kidney.

Nicolas believed that some Grawitz tumors have a powerful hemolytic action. Similar cases have occasionally been observed associated with nephritis and renal stones. It has been shown that urine has definite antihemolytic action.

Hilman,[12] under the title of "substitutio renis adiposa," referred to those processes of fat deposition in association with urinary lithiasis and, more rarely, pyelitis or pyonephrosis. Primary atrophy of the

9. Vercesi, Carlo: Sarcoma del rene fetale. Contributio allo studio dei tumori nella irta endouterina della distocie fetali, Folia gynaec. **22**:101, 1926.

10. Marion: La pyélographie dans le diagnostic des tumeurs du rein, J. d'urol. méd. et chir. **22**:310, 1926.

11. Nicolas: Methämoglobinure beim Grawitztumor, Ztschr. f. urol. Chir. **20**:212, 1926.

12. Hilman, A. G.: Ueber den Fettansatz der Nieren, Vestnik chirurgii i pogranichynch oblastej. **4**:213, 1925; abstr., Ztschr., f. urol. Chir. **20**:367, 1926.

renal substance plays the important rôle in the pathologic process; the fatty tissue develops secondarily. Hilman believed that the atrophy and fat deposition occurred in calculous pyonephrosis as a result of slow development of the process and the destructive condition brought on by shrinkage. The disease is rare, the author having noted only sixteen cases in the literature. He reported a case of his own, that of a woman, aged 56; a huge, fatty kidney, which had developed on calculous pyonephrosis, was removed. Hilman concluded: 1. The process of fat deposition in the atrophying kidney originates from the renal capsule and fatty tissue of the renal pelvis. 2. The fat metaplasia of the renal connective tissue is of little importance. 3. The clinical diagnosis is difficult, as there are no definite clinical signs. 4. The term "lipomatose paranephritis" should not be used, the old French term substitutio renis adiposa being correct.

Suprarenal Tumors.—Gibson [13] stated that a differential diagnosis of tumors of the suprarenal glands from other growths, as well as between cortical and medullary tumors of the gland itself, as a rule, can be made by their clinical manifestations. The added information gained by urologic investigation is often of decided value.

Tumors of the suprarenals give rise to three distinct syndromes, the genitosuprarenal, the Hutchinson and the Pepper. The genitosuprarenal syndrome occurs only in cortical tumors (carcinoma, hyperplasia, adenoma) and is accompanied in the female by masculine characteristics, and in the male by precocious puberty. The adult male shows no characteristic sexual alterations. Cortical tumors occur as frequently in infancy and childhood as in the adult. Hypertension is frequently associated with cortical tumors. Pigmentation occurs rarely in cortical tumors and never in medullary tumors.

The common tumors of the suprarenal medulla are of the neurocytoma or sarcoma types, which are peculiar to infancy and childhood. They occur in two forms: the Pepper, characterized by rapid abdominal enlargement due to liver metastasis, and the Hutchison, characterized by early metastasis to the orbit producing unilateral exophthalmos (already mentioned). The primary growth generally remains small and may only be discovered at necropsy. The prognosis is almost uniformly bad. The treatment is surgical and radiologic.

In a series of 47,069 cases in the University of California Hospital, nine were recorded as cases of suprarenal tumors. Of these only four were proved to be primary suprarenal tumors.

Renal Infections.—Broglio [14] stated that atrophic pyelonephritis constitutes the final stage of a process in which the ordinary trans-

13. Gibson, T. E.: The Diagnosis of Adrenal Tumors, California & West. Med. **26**:201, 1927.

14. Broglio, R.: Pyélonéphrite atrophique, J. d'urol. méd. et chir. **22**:8, 1926.

formation into pyonephrosis did not result, even though ureteral obstruction was present. The origin of the disease is obscure. He suggested as an hypothesis, that the atrophic pyelonephritis may be the final result of ascending chronic pyelonephritis in which the inflammatory process is marked in the renal parenchyma. There is preponderance of the factor "nephritis" over the factor "pyelitis," and extensive parenchymal destruction occurs before ureteral inflammation and obstruction. Pyelography is the most accurate means of investigation. It is not always possible on account of ureteral stricture and obstruction. The diagnosis is made on the evidence of pelvic dilatation without trace of small or large secondary cavities. Nephrectomy is the only procedure.

Atrophic pyelonephritis is distinguishable from chronic bilateral pyelonephritis from both clinical and pathologic points of view. The urinary symptoms are less severe and are usually not progressive; the pain is unilateral and may be more severe, and is often accompanied by evidences of acute renal infection. Usually only one kidney is affected, and, when removed, it is found to be greatly reduced in size. The atrophy may be confined largely to half of the kidney. On section marked cicatricial changes are apparent. There is often well-marked dilatation of the renal pelvis, although to a much less degree than that with primary hydronephrosis.

According to Braasch, atrophic pyelonephritis is not the end-result of the usual pyelonephritis. It can hardly be explained by primary stricture of the ureter with hydronephrosis and secondary atrophy since the dilatation of the pelvis is not sufficient to cause atrophy, and, furthermore, the atrophy is not symmetrical, but is frequently confined to one portion of the kidney. The possibility of a primary stricture of the ureter, with diffuse acute infection in the renal cortex and consequent atrophy, before the hydronephrotic sac is developed, may be considered.

Diseased kidneys are often small and difficult to find at operation. At times they are composed almost entirely of scar tissue and may not be more than 3 or 4 cm. in diameter. In spite of the apparently small amount of disease present removal of the atrophic kidney usually affords good results. In a series of cases in which operation was performed at the Mayo Clinic, improvement or cessation of vesical symptoms and improvement of the general condition have been accomplished for practically every patient.

Mercier and Pérard [15] observed a patient who exhibited marked hematuria from the left kidney about two years after nephrectomy had been performed on the right side for tuberculosis. The hematuria appeared suddenly without other symptoms. The bleeding was observed

15. Mercier, O., and Pérard, J.: Un cas d'hématurie abondante de pyélonephrite arrêtée par le cathétérisme urétéral, J. d'urol. med. et chir. **22**:304, 1926.

through the cystoscope. An injection of a few centimeters of silver nitrate stopped the hemorrhage immediately. Numerous colon bacilli were found in the urine. The authors stress the fact that from a diagnostic standpoint abundant hematuria from a healthy kidney after nephrectomy for tuberculosis does not always signify a new focus of tuberculosis. It may be caused by ordinary infection from colon bacilli.

Smirnow [16] called attention to the rarity of carbuncle of the kidney, only twenty-one true cases being recorded, including five of his own. These five showed staphylococcus infection: four, *Staphylococcus aureus* and one, staphylococcus and diplococcus of Frankel. In three cases the portal of entry was the respiratory tract, while in two it was unknown. One patient gave a history of renal trauma and ptosis.

Until recently it has been believed that such cases are secondary to infections of skin or bone. There has been no previous mention in the literature of the respiratory tract as a portal of entry, hence the hypothesis that hematogenous infection of the kidney comes from the mucous membrane of the respiratory tract.

Three of Smirnow's patients were males and two were females. Among other patients noted, fifteen were men and one was a woman.

The course is acute, but not stormy. There is constant fever, dull lumbar pain and muscle rigidity. Palpation reveals a large tender kidney. Pressure in the twelfth costovertebral angle causes pain. The urine contains pus and red blood cells. Cultures of the urine are usually sterile. Functionally, the appearance of the indigo carmine is delayed in the affected kidney. The procedure used is nephrectomy.

Renal Tuberculosis.—Forged [17] noted that the triad: sterile pyuria, albumin and the bacilli of tuberculosis, may be missing either partially or completely in advanced renal tuberculosis. Three hundred and one cases were investigated with this in mind. Only those cases were accepted in which clinical or pathologic examination revealed that the pelvis and ureter were patent. Fourteen such cases were free from albumin; among these were six cases in which tuberculous processes, which macroscopically had no connection with the pelvis, were walled off. In one or two cases with definite connection between the cavernous process and the pelvis there was entire destruction of the renal parenchyma, while in the other there was a large abscess in the lower pole which delayed drainage. In two cases, ureteral obstruction prevented drainage into the bladder; in one case the obstruction was a stone and in the other, a ureteral kink. In four other cases the reason

16. Smirnow, A. W.: Ueber Nierenkarbunkel, Ztschr. f. urol. Chir. **20**:243, 1926.

17. Forged, Jens: Nieren tuberkulose ohne charakteristischen Harnbefund, Bibliot. f. Laeger **117**:269, 1926; abstr., Ztschr. f. urol. Chir. **19**:416, 1926.

for the missing albuminuria could not be established. In still two other cases there was neither continuous nor intermittent pyuria.

[ED. NOTE.—At times the paucity of urinary symptoms is marked even if advanced renal tuberculosis is present. In rare cases an area of bullous edema simulating papillary tumor may be seen partially occluding the ureteral orifice. In other cases there is mild generalized cystitis. There is practically always diminished renal function on the infected side.

The most common type of renal tuberculosis occurring without symptoms of the bladder is the occluded type not included in Forged's series. Even in these cases of obstruction blood and pus are usually found; Braasch, in a series of sixty-seven cases of occlusion, found pus and red blood cells in all but eight. As a rule the urinary evidence of disease was not gross and urinalysis showed only a moderate number of cells.]

Ward [18] reported a most interesting case of urinary calculi composed entirely of colon bacilli. The patient, a young woman, gave a history of attacks of diarrhea. For fifteen months she had suffered from renal colic intermittently. About three months later several small soft stones were passed. A pyelogram showed a somewhat ptosed right kidney with a kink in the ureter and a filling defect in the pelvis due to stones. Later nephrectomy was performed and many stones composed of colon bacilli were found.

Soft concretions are rare, and most of the soft stones reported are composed of fibrin-like material. Israel, in his recent book, mentions references to four cases similar to the one recorded.

Syphilis of the Kidney.—Isaac-Krieger [19] asserted that nephrosis is the most significant of syphilitic diseases of the kidney. It consists of degenerative changes of the epithelium in the collecting tubules. The acute form is characterized by generalized edema and transudation, albuminuria reaching as high as 50 per cent and lipoiduria; hypertension and changes in the eyegrounds are usually absent. There is no increased nitrogen retention in the blood. With immediate treatment, recovery is rapid. Without treatment the condition passes into the chronic form. Distinction from glomerulonephritis is made by the absence of increased blood pressure and hematuria. Dietetically, there need be no decrease in the intake of albumin, but the amount of salt must be limited. Small doses of arsphenamine (0.15 Gm.) are given. Mercury is not used in the treatment, but bismuth may be given.

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18. Ward, R. O.: Urinary Calculi Composed of Bacteria, Brit. J. Surg. **14**: 230, 1926.

19. Isaac-Krieger, Karl: Die Lues der Nieren, Ztschr. f. ärztl. Fortbild. **23**: 143, 1926; abstr., Ztschr. f. urol. Chir. **20**:427, 1926.

The disease gradually develops into chronic nephrosis without edema; there may be slight edema of the ankles with continual ascites. The complications are bronchitis, sepsis and peritonitis. Further development may lead to amyloid degeneration or contracted kidney. In the latter condition it is not markedly different from true contracted kidney. At this stage hypertension, polyuria, nocturia, cardiac hypertrophy, edema, albuminuria and scanty urinary sediment may be seen. Antisyphilitic treatment must be handled carefully at this stage.

Renal Cysts.—Löffler [20] stated that retention cysts of the kidney are either single or multiple and are often found by the pathologist. As they may not cause symptoms they are less often found by the clinician. The larger cysts sometimes fill the abdominal cavity and cause symptoms by pressure on adjacent organs. They may not, however, cause symptoms; the smaller cysts may give much trouble.

The cysts are usually in the lower pole, less often in the upper pole, and seldom on the convex border or sides of the kidney.

Löffler cited four cases. In the first case a large cyst in the lower pole of the left kidney caused increased mobility of the kidney and compressed the colon and stomach. In the second case there were two cysts on the convex border and another "the size of an apple" in the lower pole of the left kidney. In the third case the solitary cyst "the size of an orange" was at the lower pole of the right kidney pressing on the colon. In the first and third cases, the diagnosis was made by palpation, while in the second case the mass was thought to be a renal tumor. In the fourth case there was renal colic with deficient function from the left kidney. At operation the kidney was found to be normal, but a dark, livid "cherry-sized" tumor projected from the hilum, compressing the renal pelvis. It was thought to be malignant, and nephrectomy was performed. Pathologically, it was a small renal cyst which had grown out from the hilum. Similar cases are rare; the author found only two in the literature (Israel and Herrieck). The usual procedure is nephrectomy. Löffler believed that if function is good, the cyst should be resected, as was done in two of his cases.

[Ed. Note.—Large renal cysts, which may occur at either pole of the kidney, usually the lower, may be resected readily and rarely cause marked impairment of renal function. Some of these cysts shell out of the kidney and leave flaps of renal substance that approximate readily to form a normal appearing kidney. Cysts of long standing usually have fairly thick walls and at times may be removed intact without rupture.

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20. Löffler, Leopold: Zur Klinik der Nierencysten, Ztschr. f. urol. Chir. **20**:407, 1926.

Renal cysts cause pyelographic deformity similar to that of an extrarenal tumor; there may be obliteration of one of the calices, but the calix is rarely drawn out or attenuated as occurs with renal neoplasm. Usually few symptoms suggestive of a renal lesion are present.]

Tests of Function.—Damski [21] stated that pus in the renal region, originating primarily by way of the vascular system and secondarily from various diseases of the abdominal organs and the kidneys, belongs to that field of surgery which has not been satisfactorily explained. The etiology is still obscure and it is often extremely difficult to make an exact diagnosis. The relationship of perinephritic abscess to the various renal diseases which may necessitate nephrectomy is important. Many surgeons merely drain the abscess without further exploration.

After citing several cases, Damski concluded that: (1) in cases of perinephritic abscess with normal urine, urologic investigation is indispensable; (2) the amount of urine from the diseased kidney does not always indicate the pathologic condition of that kidney; following the opening of such a perinephritic abscess, the kidney should be carefully explored; (3) in cases in which exploration is not feasible, following the disappearance of fever and other toxic signs, urologic examination should be carried out to determine the exact status of such a kidney, and (4) any abnormality of the urine from the diseased renal area must be given due consideration, in comparison with the urine from the normal side. Damski stated that there may be diminution of the output of indigo carmine from the kidney.

Blanc [22] said that the phenolsulphonphthalein test is universally recognized as of considerable value in the study of renal function. The test must be carried out accurately if surgical procedure is to be decided, or if the function of each kidney is to be determined. Blanc favors the intravenous injection, since it is more accurate than the subcutaneous. Two conditions are essential for accurate results: all of the injection must pass into the vein and exactly 6 mg. of phenolsulphonphthalein should be injected. Blanc proposes the use of a graduated syringe and suggests diluting the 6 mg. of phenolsulphonphthalein to 4 cc. The results thus obtained are constant. A healthy kidney should eliminate from 30 to 35 per cent in seventy minutes; the total elimination should therefore be from 60 to 70 per cent.

Hinman and Vecki [23] stated that under gradually increasing pressure in the renal pelvis there is a back flow of the pelvic contents into the

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21. Damski, A.: Einige Bemerkungen über den Wert des Ureterenkathaterismus und der Indigcarminprobe bei paranephritischen Eiterungen, Ztschr. f. urol. Chir. **20**:401, 1926.

22. Blanc, A. H.: À propos de la technique de l'epreuve de la P. S. P. en chirurgie urinaire, J. d'urol. méd. et chir. **22**:17, 1926.

23. Hinman, Frank; and Vecki, Morrell: Pyelovenous Back Flow: The Fate of Phenolsulphonphthalein in a Normal Renal Pelvis with the Ureter Tied, J. Urol. **15**:267, 1926.

renal vein, and the back pressure producing it is less than the excretory pressure. When this back flow has once been established, it will continue under low pressure. In experiments on rabbits, 2 cc. of phenolsulphonphthalein was injected slowly into the renal pelvis and the ureter ligated. Three of these animals were killed after twenty-four hours, three after forty-eight hours, two after ninety-six hours, and three after one hundred and sixty-eight hours. The bladder was catheterized in each case at the end of twenty-four and forty-eight hours and the amount of dye estimated. It was found that practically all the dye disappeared from the pelvis within four days and that little was left after two days. These observations indicate that an active flow of the dye occurred through the completely tied off renal pelvis. In conclusion, Hinman and Vecki stated that the content of a closed hydronephrotic sac is neither cumulative nor stagnant, but undergoes a continuous change, fresh material being removed by active reabsorption which occurs mainly through pyelovenous back flow.

Fluoroscopy.—Cross [24] advised the injection of opaque mediums for pyelograms under the guidance of vision. He believed that greater accuracy is maintained by injecting the kidney under observation with the fluoroscope, and since one may observe the flow down the ureter while the injection proceeds, there is less danger of overdistention of these delicate structures. The mobility of the kidney is easily ascertained, the change from the normal action is observed, and when stones that have not been suspected are encountered, turning the patient as the filling is in progress will give valuable information in the interpretation of the roentgenograms.

Legueu [25] stated that pyeloscopy, fluoroscopy of the renal pelvis, is of more value than pyelography in diagnosis. He has used this procedure in more than 700 cases and believes that the correct use of it requires considerable experience. The technic is well established: the catheter is inserted into the pelvis and a syringe injection of sodium iodide carefully and slowly made; the progress of the injection is noted under the fluoroscopic screen. He said that there are two different types of pelvic contractions, "contractions en masse" and "contractions speciales," the pelvis and ureters acting similarly to the stomach. The evacuation of the pelvis lasts from two to ten minutes, the short contractions being produced at a rate of from five to six a minute. Legueu suggested that there may be a pyelo-ureteral sphincter which opens intermittently, the ureters having automatic contractions. From a

24. Cross, W. W.: The Fluoroscope as an Aid to Making Pyelograms, J. Urol. **16**:37, 1926.

25. Legueu: La physiologie normale et pathologique etudiée à l'aide de la pyéloscopie, Scalpel **79**:1027, 1927.

pathologic standpoint, Legueu found that in certain types of hydronephrosis evacuation does not occur; the retention is complete, whereas in other cases the retention is incomplete and retarded. In some cases hyperkinetic movements with spasmodic contractions are observed; hydronephrosis in such a case might be explained as being produced by a neuromuscular disturbance of dynamic origin, and mechanical influence would play only an accessory rôle. The study of the pelvic musculature is also of importance in establishing the prognosis of pyelonephritis due to the colon bacillus; if the infected secretion is not kept in the pelvis through complete retention, the prognosis may be more satisfactory.

URETER

Tumors.—Stewart [26] asserted that tumors of the ureter are usually of the papillary form. Any portion of the ureter may be affected, although there is evidently a predilection for either the upper or the lower portion. The symptoms produced are not pathognomonic and are the same as those engendered by renal neoplasm, namely, hematuria, pain, and sometimes renal enlargement because the tumor obstructs the ureter and causes hydronephrosis. Accurate diagnosis is usually difficult, but considerable aid is obtained from the employment of ureteral catheterization and pyelo-ureterography. It is important to determine the downward extent of the tumor, with special reference to the possibility of multiple growths. Radical operation is indicated. In most instances, nephro-ureterectomy, either complete or partial, is the method of choice.

Stones.—Rathbun [27] pointed out that a large number of ureteral calculi pass spontaneously. Those which do not pass spontaneously and which show a tendency to lodge in one portion of the ureter possess greater potentiality for harm and require more careful consideration than those that are confined to the renal pelvis or one of the calices. It is often difficult to decide when conservative treatment should be used. The small stones will usually pass but the large ones usually require surgical intervention. Rathbun advised dilatation with ordinary silk elastic bougies and catheters. He disapproved of metallic mechanical dilators and preferred fulguration to enlarge the ureteral orifices to the use of cutting scissors because the latter type of incision often closes too quickly.

Rathbun considered it a real problem to answer the question: How long are we warranted in using these conservative measures? This depends on several factors, one of which is the position, shape and mobility of the calculus. He is more hopeful in such cases if the stone

26. Stewart, R. L.: Primary Tumors of the Ureter, Brit. J. Surg. **13**:667, 1926.

27. Rathbun, N. P.: The Management of Ureter Calculi, J. Urol. **16**:255, 1926.

is noted just above the sacral promontory or just above the intramural portion, particularly if roentgenograms show variation in position at different times. He is less optimistic if the stone is noted about midway between the bladder and the brim of the pelvis, particularly if repeated roentgenograms that are carefully studied do not show any variation in position. He has found the calculus so firmly embedded in the mucosa of the ureter that it was difficult to extract it through an open incision, and is confident that no amount of dilatation would have influenced its position in the slightest degree.

Ectopic Openings.—Herbst and Polkey [28] reported the case of a young girl who had suffered from incontinence since birth, because a ureter from an extra pelvis of the right kidney opened into the vagina. Heminephrectomy effected a cure. They noted that Kilbane reported ninety-eight cases from the literature besides two of his own.

The condition occurs with about equal frequency in the two sexes, although the male presents fewer symptoms. Incontinence, both diurnal and nocturnal, associated with the normal act of micturition is usually noted. The history of incontinence dates back to infancy, and in most cases is constant, except in a few in which the ureter passed under the sphincter in such a way that incontinence is controlled intermittently. Male patients do not experience this incontinence since the openings are above the external sphincter, usually above the level of the colliculus. In 75 per cent of the reported cases the ectopic opening belonged to a supernumerary ureter, and this ureter always drained the upper pelvis of a double kidney.

Herbst and Polkey believed that exploration and heminephrectomy offer a valuable method of procedure for this anomaly, because the majority of such ectopic ureteral orifices belong to supernumerary ureters that drain a part of a double or fused kidney. Many of the ureters are distended and infection of the part of the kidney which they drain makes implantation of this group an uncertain method. In cases in which the lower end of the ureter is accessible and a study of the upper portion of the urinary tract fails to show any marked dilatation and infection, some type of implantation may be indicated.

[Ed. Note.—Early in embryonic life the proximal end of the ureter opens into the lower end of the wolffian duct, but under normal conditions, at about the sixth week, the ureter and duct divide and open separately. If the ureter does not become detached from the duct and accompany it in its downward course, the ureteral openings may be found in any of the organs developing from the urogenital sinus.

Hartman and Copenhagen analyzed thirty-seven cases in which the ureters opened extravesically; fourteen were supernumerary. The

28. Herbst, R. H., and Polkey, H. J.: Ectopic Ureteral Openings, J. Urol. **17**:61, 1927.

openings were in the urethra in six, in the vagina in eight, in the vestibule of the vagina in twenty-one and in Gartner's duct in two.]

Fronstein [29] stated that the stump of a ureter remaining after nephrectomy produces peristaltic waves. These have been observed as long as twelve years after the kidney was removed. These waves are able to express pus from the ureteral stump into the bladder.

Fronstein believed that aside from strictures and stones, the tone of the ureter is a factor. A ureterogram should be made in all cases, and if negative the usual operation of the kidney may be performed. If any of the foregoing factors are present, ureterectomy should be performed.

Empyema of the ureteral stump is rare; Kummell reported four in 286 nephrectomies and Israel four in 900 nephrectomies. Hyman reported three cases. Strictures or stones were usually present. Fronstein observed three cases in twenty years. The duration may be long, ranging from six to twenty-three years; he believes, therefore, that the condition sometimes occurs and is not found.

The procedure accepted by most observers is complete extirpation. Fowler opens the sack and drains it by sewing the drain to the edges of the wound.

PROSTATE

Hypertrophy.—Cohen, Dodds and Webb,[30] because of lack of uniform views on the value of tests of renal function in relation to prostatectomy, investigated a series of cases particularly in reference to analysis of the blood. It was found that the nonprotein nitrogen content and uric acid content of the blood formed the best guide to prognosis. The upper limit of safety for the complete operation of prostatectomy was found to be 50 mg. of nonprotein nitrogen and 3.5 mg. of uric acid for each hundred cubic centimeters. Experience has shown that if there is an increase over this, it is advisable to perform preliminary suprapubic cystotomy. Enucleation can be carried out within the limits of safety. The urea content of the blood is much more unreliable than the nonprotein nitrogen and uric acid contents. A high urea content must always be regarded as a serious sign, but a low urea content cannot always be regarded as an indication of normal renal function. Laboratory data should always be considered in combination with the clinical data.

Pasteau [31] classified diseases of the prostate and the indications for treatment. Hypertrophy necessitates treatment when it causes retention.

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29. Fronstein, R.: Das Empyem des Harnleiterstumpfes, Ztschr. f. urol. Chir. **20**:183, 1926.

30. Cohen, I.; Dodds, E. C., and Webb, C. H. S.: Observations Bearing Upon the Operation of Prostatectomy, Brit. J. Surg. **13**:656, 1926.

31. Pasteau, O.: Indications operatoires des prostatectomies, J. méd. franç. **16**:3, 1927.

If the urine is clear and the retention is chronic, prostatectomy is indicated, especially if there is also vesical distention, and catheterization should not be employed. If the urine is infected, catheterization is necessary and should be carried out before operation. There are two types of prostatic stones, the urethroprostatic and the intraprostatic. Large intraprostatic stones are an indication for prostatectomy. Stones of the bladder are much more rare since prostatectomy, which relieves urinary retention, is now more frequently performed. Surgical intervention is indicated in malignant tumors of the prostate, unless there is diffuse carcinosis.

Pasteau reviewed the symptoms which usually lead to prostatectomy. In cases of chronic retention with infection but without distention, the need for operation is not immediate and preoperative treatment should be employed. Operation should be performed at once in cases of acute retention, and in some cases of severe prostatic bleeding, prostatectomy may be a life-saving procedure.

The perineal route should be used only occasionally, for example, in cases of serious urinary infection or in malignant conditions. The suprapubic route should be used. In most cases, the two stage operation gives a much better prognosis than the one stage. Pasteau advised an interval of a month after cystostomy before enucleation of the prostate.

Bumpus [32] reported the results of the use of the punch operation in 114 of his cases at the Mayo Clinic. In seventy-two cases, the Caulk cautery punch was used. The functional results were better because of the large amounts of tissue removed. Two serious difficulties were encountered, however: delayed bleeding and continued febrile reaction. It is considered that these inconveniences more than outweigh the difficulties of immediate hemostasis encountered with the knife puncture of the Young and Braasch type. The poor results in early cases in which the knife punch is used should be much more than overcome by the modification of the Braasch punch, with which much larger portions of tissue may be removed. Punch operations are ideal in the median-bar types of obstruction. Bumpus does not advise the use of a punch in cases in which the lateral lobe of the prostate occurs.

Legueu [33] used the roentgen ray intensively in a series of cases of prostatic hypertrophy, but radical operation usually had to be instituted to relieve difficult urination. Occasionally irradiation was followed by marked induration of the prostate and perineum which might be confused with carcinoma. In one case in which this occurred operation was deferred for six months, during which time most of the induration was

32. Bumpus, H. C.: Results of Punch Prostatectomy, J. Urol. **16**:59, 1926.

33. Legueu: De la radiothérapie de l'adénome prostatique, J. d'urol. **21**:170, 1926.

absorbed. Operation revealed an intensely inflamed prostate. Legueu believed that roentgen-ray treatment brought on definite malignant changes in one case. As a result of his experiments he believed the roentgen ray to be useless, dangerous and entirely incapable of even modifying the course of the disease.

De Beaufond [34] divided cases of prostatic hypertrophy into two groups, the recognized and the unrecognized. Unrecognized hypertrophy causing residual urine is a treacherous form. In the recognized types intervention is not always indicated; the patient may have secondary congestion or prostatitis and should be treated by massage. In cases in which intervention is necessary various conditions must first be corrected. If patients have uremia, drainage is usually required. Perineal operation should be performed on elderly, weak patients. In aseptic cases in which there is retention, catheterization should be carried out with aseptic precautions; if catheterization must be frequent, the bladder should be drained.

Marion [35] stated that an intervesicoprostatic diaphragm may develop even after successful prostatectomy. Sometimes it is possible to insert only a curved filiform catheter. This diaphragm is the result of exaggerated development of the spur which is most often left between the bladder and the space from which the prostate has been removed. Marion observed such a diaphragm on reopening a bladder because of retention following prostatectomy. The bladder appeared to be composed of two cavities, a large upper one and a small lower one separated by a diaphragm which almost entirely closed the bladder. Such a diaphragm is the result of faulty technic in operating; when the periurethral adenoma projects far into the bladder it is necessary to tear the bladder around the adenoma, instead of the mucous membrane covering it; if this is not done a floating flap is left which may constitute only a spur at first, but which later develops into a diaphragmatic flap which separates the bladder and the prostatic cavity. If a loose flap or edge of mucosa remains after removal of the prostate it should be torn with the finger at its juncture with the wall of the bladder A postoperative diaphragm of this type must be distinguished from aberrant prostatic adenoma or a stricture consequent to a tear of the urethra far below the adenoma. Marion devised a special instrument to insert through the urethra to cut these flaps or diaphragms; it consisted of a "benique" sound containing two blades. He used it successfully in four cases. If it is impossible to open the diaphragm through the urethra the bladder should be opened and the diaphragm cut.

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34. De Beaufond: Les premiers soins medicauz aux prostatiques, J. méd. franç. **16**:8, 1927.

35. Marion, G.: Le diaphragme intervésico-prostatique après la prostatectomie, J. d'urol. méd. et chir. **22**:257, 1926.

Cassuto,[36] in fulgurating a median prostatic lobe with a MacCarthy urethroscope, noted a sudden violent explosion inside the bladder. As the bladder did not seem to be ruptured, he waited, ready to operate if peritoneal or other symptoms became alarming. A cystoscopic examination performed on the eighth day disclosed a slightly edematous bladder with large stellate cuts on all its surface. Cassuto believed that the gas accumulating from the carbonization of the tissues exploded. Saint Cene, who reported two analogous cases, found that the explosion took place on fulgurating near the upper surfaces of the bladder where gas accumulates.

Michon [37] stated that occasionally cases are noted in which all the signs and symptoms of prostatic obstruction are exhibited and in which, nevertheless, it is clinically impossible to find the suspected enlargement. Symptoms such as dysuria, stagnation of urine, complete or incomplete retention and distention are not found alone in association with large prostates; there is no definite or constant relationship between the size of the prostate and the extent of the symptoms present. However, retention in the acute form is exceptional in cases in which there are prostatic symptoms but no enlarged prostate; in contrast to this, chronic, insidious retention, revealing itself only when there is distention, is not infrequently an accompaniment of the so-called prostate sans prostate. It is impossible in some cases with the most accurate examination and with the help of endoscopy, to discover the lesion. Histologic examinations alone, in spite of the absence of any objective signs, will permit the inclusion of this type of case in the group of prostatic cases and will suggest the kind of procedure that is used when the prostate is definitely hypertrophied, namely prostatectomy.

In the type of case presenting all the signs and symptoms of prostatism, even though the prostate is not large, prostatectomy should be performed. Even though it may not be apparent, there is usually a local lesion present and prostatectomy will relieve all the symptoms.

Thomas [38] outlined the preoperative care in prostatic cases as comprising drainage of the bladder and renal decompression, physical treatment and drugs when necessary, determination of the operability of the patient and determination of the best method of surgical intervention.

In practically all cases of prostatic obstruction with either complete or partial retention of urine, the factor of primary and paramount importance is drainage of the bladder in order to relieve urinary backpressure on the kidneys. This procedure may be satisfactorily carried out either by intermittent or continuous catheterization or by cystotomy.

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36. Cassuto, Augusto: Explosion dans la vessie au cours d'une électro-coagulation, J. d'urol. méd. et chir. **22**:263, 1926.

37. Michon, Louis: Prostaties sans prostates, J. méd. franç. **16**:14, 1927.

38. Thomas, B. A.: Preoperative Care of Patients with Prostatic Obstructions, J. Urol. **17**:87, 1927.

The much discussed question of drainage by catheter versus cystotomy or so-called one-stage versus two-stage prostatectomy seems still to be far from solution. Thomas reserves cystostomy for only a few patients, about 13 per cent.

Avoidance of constipation, forcing fluids and relief of back-pressure are the chief measures employed. Thorough physical examination should be made in all cases. The routine practice of Thomas in a study of renal function is the determination of the index of elimination of phenolsulphonphthalein or indigo carmine a day or two after admission and also on the same day the determinations of the blood urea nitrogen, blood sugar and coagulation time of the blood are made. Determination of the coagulation time will occasionally help one detect a bleeder. Treatment directed to hyperglycemia, when it exists, will facilitate convalescence. If the patient is found to have nitrogen retention, the blood urea test is repeated weekly. Values up to 20 mg. for each hundred cubic centimeters of blood are regarded as excellent prognostically, from 20 to 30 mg. as borderline, but not prohibiting operation if everything else is satisfactory, and over 30 mg., as contraindicative of prostatectomy at that time. The index of elimination of any of the dyes, phenolsulphonphthalein having the preference for colorimetry in most laboratories, is probably sufficient. It gives a better idea of the stability of the renal function, which is the factor with which we are most concerned, and is easier of application than any of the biochemical blood tests.

Low blood pressure is as bad as high blood pressure. A patient with systolic pressure of less than 110 must have a diastolic of more than 60, and a patient with diastolic pressure of less than 60 must have a systolic of more than 110. In such cases digitalization may turn the tide in favor of stage operative intervention.

[ED. NOTE.—One-stage prostatectomy is the operation usually preferred. It permits visualization, accurate hemostastis and thorough removal of the gland. Consequently, in large clinics in which the operations are performed by highly skilled surgeons, preliminary drainage is carried out by means of a urethral catheter. On the other hand, many urologists consider the two-stage operation, with preliminary cystostomy and later removal of the gland, the safest procedure. In careful hands, with an accurately controlled preliminary period of observation, excellent results are obtained by either method. In the present period of accurate urologic diagnosis together with the series of excellent renal functional procedures, death from uremia following prostatectomy is rare.]

Kinney [39] believed that postoperative care in prostatic cases should start with careful preoperative study and the proper choice of anesthesia.

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39. Kinney, W. H.: Post-Operative Care of Patients After Prostatectomy, J. Urol. **17**:93, 1927.

Careful operative technic with as little mutilation as possible of the surrounding structures and with attention to hemostasis, by thorough packing thereby preventing secondary hemorrhage, is of utmost importance. Fluid should be forced by hypodermoclysis or other methods. The cardiovascular system should be watched carefully. Cleanliness of the operative wound during convalescence and prophylaxis against infection of the genito-urinary tract are necessary. Elimination by all the natural means must be watched and encouraged.

Infection.—Henry [40] asserted that suppurative prostatitis should be treated surgically as early as possible. This avoids serious complications which might develop into a comparatively benign condition. Small abscesses situated on the anterior portion of the gland near the urethra may be treated medically. Massage should not be carried out; vaccines are useless. The abscess may be evacuated surgically in several ways. In the urethral route a finger introduced into the rectum pushes the prostate forward, while a rigid sound, placed in the urethra, is directed with force through the posterior wall of the prostatic urethra. This method is dangerous, but it may be used successfully in cases in which the infection is entirely intraprostatic. In the rectal route an incision is made through the rectal mucosa; this method may be used in abscesses that protrude on the side of the rectum and do not open into the urethra.

The perineal route in operating is the most satisfactory; a urethral catheter is inserted to be used as a guide. Either a transverse or a vertical perineal incision may be used. The rectum is stripped from the posterior surface of the prostate and the abscess opened. All pockets are drained and packed with gauze. This method assures a successful outcome, usually without complications. If the abscess is opened into the urethra and fistula results, insertion of a permanent urethral catheter permits the fistula to heal.

Lavenant [41] stated that conservative or medical treatment does not suffice for all types of prostatitis. Patients who have prostatitis of the sclerous type with a vesical bar causing retention should be treated by the Bottini method or by fulguration; those who have prostatitis with the formation of stones should be treated surgically. Certain surgeons have been able to remove prostatic stones through the urethra, but this leaves the prostate as a focus of infection; it should be removed entirely. Following suprapubic prostatectomy in some cases the remaining prostatic tissue may be treated by ordinary conservative methods, but occasionally a secondary perineal prostatectomy is necessary for complete cure.

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40. Henry, Robert: Les grandes infections de la prostate. Abces de la prostate et phlegmons periprostatiques, J. méd. franç. **16**:26, 1927.

41. Lavenant, A.: Les prostaties aigues et chroniques et leur traitement, J. méd. franç. **16**:19, 1927.

Stones.—Kretschmer [42] reviewed seventy-six cases of true prostatic calculi. The youngest patient was 21, the oldest, 76. Thirty-three gave a history of antecedent gonorrheal urethritis. A number of patients presented themselves because of pain caused by stone in the kidney or ureter. Other patients were free from all symptoms and signs of urinary or venereal disease. Still other patients complained of lesions that are generally attributed to foci of infection, and the investigation to rule out the prostate and seminal vesicles as etiologic factors disclosed stones in the prostate. These patients complained of lumbago, sciatica, neuritis, arthritis and rheumatism. Another group was characterized by the presence of referred pain or symptoms, such as pain in the perineum, pain in the sacrum, suprapubic pain, irritation at the neck of the bladder, pain and spasm in the rectum and a full feeling in the rectum, the most frequent referred symptoms being suprapubic and perineal pain. In still another group, the patients had had postgonorrheal infection in the prostate and seminal vesicles, for which they had been treated as a routine measure by massage, sounds, irrigations and instillations.

Frequency of micturition, dysuria and nocturia were present, but these symptoms were in no way peculiar to patients with stones of the prostate. Sexual symptoms were less common and consisted of loss of desire and impotence.

Rectal examination revealed a change in the consistency of the prostate; at times it was extremely hard and suggested a malignant condition. In some cases stones could be palpated through the rectum, crepitation being felt.

BLADDER

Nerve Control.—Elsberg [43] stated that the nervous control of the bladder is under three mechanisms. The sympathetic connector fibers leave the spinal cord by the two lower thoracic nerves and the two upper lumbar nerves (Holmes and Walsh), or perhaps by the four upper lumbar nerves, and pass, with relays, to the hypogastric nerves and the wall of the bladder. The second nervous connection is derived directly from the second, third and fourth sacral nerves, and passes to the wall of the bladder by way of the nervi erigentes. The third, and perhaps voluntary, element of micturition is passed by the pudic nerves to the urethral muscles.

Voluntary micturition and evacuation of the bladder are in some way controlled by the brain through the nervi erigentes and pudic nerves, and result from the simultaneous contraction of the musculature of

42. Kretschmer, H. L.: True Prostatic Calculi, Surg. Gynec. Obst. **44**:163, 1927.

43. Elsberg, C. A.: The Frequency and Character of Bladder Disturbances in New-Growths of the Brain and Spinal Cord, Ann. Surg. **84**:509, 1926.

the bladder and relaxation of the sphincter muscles of the neck of the bladder and urethra. Difficulty in the expulsion of urine, besides being caused by mechanical obstruction, may be due to diminished muscular power of the bladder, to increase in the tone of the sphincter muscles or to a combination of these two factors, resulting from a disturbance in nonsympathetic nervous control, while true vesical incontinence in the conscious person is probably rare except when there is interference with all three mechanisms. The control of the bladder, however, may be exercised by the spinal cord when part of the cord has been entirely separated from the higher centers, although such activity of the bladder is purely reflex and not under voluntary control.

Elsberg discussed disturbances of the bladder in cases of tumor of the brain, which occur in only one fourth of the cases, if those due to clouding of consciousness or psychic defect are excluded. In 165 patients with verified tumor of the brain, 60 had some disturbance of normal micturition, and 39 (23 per cent) had occasional or continued incontinence. Sixty-nine of the 165 patients were more or less disturbed mentally. In tumors of the frontal lobes mental disturbances were, of course, common, and in most of these cases some variety of vesical disturbances was present, incontinence being frequent. On the other hand, incontinence was infrequent when the growth was in some other portion of the brain. Excluding patients in stupor, coma, or with marked mental changes, urinary disturbances were no more frequent with subcortical than with cortical growths.

In tumors of the spinal cord disturbances of the bladder are noted much more frequently in the extramedullary, extradural, and conus and cauda types. In 80 per cent of the extramedullary, 84 per cent of the extradural and 60 per cent of the intramedullary growths such disturbances were present, but a tumor outside of the substance of the cord is more likely to cause disturbance than one within the substance. There is no particular segment of the cord especially concerned with control of the vesical sphincter. The lower the compression of the tumor is on the cord, however, the more common are the disturbances of the bladder.

Disturbances of the bladder usually appear late with tumors of the spinal cord, except in cases of extradural primary or secondary malignant disease in which the advance is rapid. Even if the tumor is in the sacral segments of the cord, where the nerve centers of the bladder lie, it is surprising that symptoms do not occur for at least a year. If tumors are within the substance of the cord, vesical disturbances, while much less common, appear earlier than with extramedullary growths.

The type of disturbance noted varied with the consistency of the tumor, the amount of compression of the cord and the rate of growth. Other things being equal, if the symptoms of the spinal cord have

lasted less than six months, difficulty in emptying the bladder is the most frequent; if they have lasted from six to twelve months, difficulty in urination or incontinence is frequent, and when the symptoms and signs of spinal compression have lasted several years or more, incontinence due either to overflow or to true paralysis of the sphincter muscle is most frequent.

After removal of the tumor improvement in vesical control may occur rapidly. During the period that the patient is recovering vesical control, the contraction of the bladder is imperfect, and in consequence a number of ounces of residual urine are retained. Elsberg noted that the feeling of fulness in the bladder returns quickly if patients improve, as a rule before the return of somatic sensation. If prolonged pressure of the tumor has made recovery impossible, a pure spinal automatic control may appear in a few months.

Attention is called to the fact that we should not overlook purely genito-urinary disorders that may be associated with disease of the central nervous system and cause symptoms entirely independent of those due to lesion of the nerve.

[ED. NOTE.—This article clears up a number of features concerning which urologists are frequently confused. While the act of micturition is not altogether explainable so far as detailed nervous mechanism is concerned, the ideas presented by Elsberg serve as a good basis for the practical explanation of the various features of the so-called cord bladder. Urologists often think only of the relaxed sphincter, vesical anesthesia, weak stream and fine trabeculation, which give the picture of the paretic bladder, without considering carefully the type of nerve lesion. As Elsberg notes, there is great opportunity for collaboration between the cystoscopist and the neurologist in correlating the disturbance of vesical mechanism with various types and sites of tumors, during their growth and after their removal.]

Neoplasms.—Harris,[44] in a 6 months female fetus, found a "pear shaped, apple sized" tumor which had pushed itself into the vesical neck. Histologically, it was composed of myxomatous connective tissue and was covered with plain epithelial cells. The musculature of the bladder was somewhat hypertrophied.

Perforation.—Boss [45] recalled that the occurrence of spontaneous rupture of appendiceal abscess was well known to the surgeons of the nineteenth century; it was regarded as a good sign. Today rupture into the gastro-intestinal tract, bladder and other hollow organs is forestalled by early diagnosis and drainage.

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44. Harris, H. A.: A Mesodermal Tumour of the Trigone of the Bladder in a Female Foetus of the Sixth Month, J. Anat. **60**:329, 1926.

45. Boss, William: Perforation von appendicitischen Eiterungen in die Blase, Ztschr. f. urol. Chir. **20**:215, 1926.

Boss reported two cases of appendical rupture into the urinary bladder. The process usually is a slow one, which frequently adjusts itself. The pelvic fascias do not long resist an abscess and permit it to bore through. The contact of the pus with the vesical wall tends to cause retention and pain when the bladder empties. The vesical wall becomes thinner, helped by the opposing pressure of the urine, and finally rupture occurs. The differences of pressure causes disturbances in the circulation of the vesical wall and therefore enhances the tendency toward rupture. There may be no indication of the condition or there may be severe characteristic symptoms. There may be marked frequency and urgency with chills and fever for the first few days, leading occasionally to retention.

Cystoscopy does not show generalized cystitis; a circumscribed inflammatory reaction and bullous edema in the region of the perforation may be seen only occasionally. On the contrary, fistulas from adnexal perforations can be seen clearly. The urine contains fecoliths, fecal material, plant cells and muscle fibers, and has a fecal odor. Charcoal may be given by mouth and found in the urine, thereby demonstrating the fistulous connection.

The perforations usually heal spontaneously. They have been known to persist for as long as ten years. The bladder does not need particular attention.

Cecil [46] reported a case of sarcoma of the bladder in a man, aged 27. After suprapubic cystostomy and bilateral transplantation of the ureters to the rectum, total cystectomy was performed. The patient remained well for a year and nine months when a growth recurred in the abdominal wall and was excised by cautery shortly before the case was reported. Cecil also reviewed the literature, giving details of 193 cases of sarcoma of the bladder. From these cases he concluded that the gross appearance is not characteristic enough to distinguish it from other tumors. The tumor is usually situated on the base, trigone or vesical orifice, although it is found on the lateral and anterior walls more frequently than are epithelial tumors. Microscopically, it assumes all the varieties of sarcoma and has a marked tendency to invade the surrounding structures. It grows rapidly, and not infrequently multiple tumors are noted. Patients usually are young or past middle age, but they may be all ages. The tumors do not tend to metastasize and metastasis occurs late if at all. Hematuria is not constant. It is not even always present, and if present, is usually a late manifestation. Other symptoms also appear late. The diagnosis depends entirely on microscopic examination of the specimen. Resection is the method of choice in early cases. Irradiation has not been given sufficient trial, but it will probably prove inadequate. In most cases total cystectomy offers the only chance of cure.

46. Cecil, H. L.: Sarcoma of the Bladder, J. Urol. **16**:471, 1926.

Schmitz and Laibe [47] reported a series of fifty-two cases of inoperable advanced primary carcinoma of the urinary bladder in which the treatment consisted of radium, cautery and radium or roentgen rays, and roentgen rays alone. Satisfactory results were obtained with the massive, short-wave roentgen ray. The authors explained these good results by the carrying distribution of the intensity of radium and the roentgen ray and by the sensitiveness of the carcinoma to irradiation. They concluded that the short-wave roentgen ray applied according to modern methods is efficient in arresting the cancerous growth and in restoring the function of the bladder to normal.

Heilmann [48] described a pathologic anatomic lesion in the bladder of a woman, aged 73. There were numerous small white nodules the size of a pin, with a hemorrhagic halo, the center of which was sunken. There was also generalized cystitis. The urine was weakly acid and contained pus cells and colon bacilli. Microscopically, some of the nodules appeared as lymph follicles, sometimes with a large budding nucleus. Most of the follicles showed pathologic change; the capillaries were dilated and in the middle of the node were large, pale epithelioid cells undergoing degeneration, among which could be found granular masses. Some cells contained inclusions. A dense ring of lymphocytes could be seen about the nucleus. The larger plaques consisted chiefly of large polar cells. The flat epithelium of the wall of the bladder was missing over some of these plaques and some were necrotic. The entire picture suggested nodular cystitis and malakoplakia. The author believed that the malakoplakia developed from nodular cystitis.

Briggs and Maxwell [49] reported three cases of urinary leukoplakia. They also reported fifteen cases (five renal and ten vesical) that had been abstracted in the literature. If the urinary tract as a whole is considered, the condition is more common in men; however, the kidneys of men and women are affected equally. The renal pelvis is probably affected oftener than the bladder, in spite of the fact that vesical leukoplakia can be diagnosed by cystoscopy alone, whereas the renal condition usually requires nephrectomy or necropsy for diagnosis. The condition may occur at any age. The average age at the time of diagnosis in the eighty cases was 41 years. It occurred earlier in the renal cases. Leukoplakia is probably present years before it is recognized; in each of the three cases reported by Briggs and Maxwell, urinary symptoms had been present for thirteen years.

47. Schmitz, Henry; and Laibe, J. E. F.: Roentgen-Ray Treatment of Inoperable Carcinomas of the Urinary Bladder, J. A. M. A. **87**:1541 (Nov. 6) 1926.

48. Heilmann, P.: Ueber Cystitis nodularis und Malakoplakie, Beitr. z. path. Anat. u. z. allg. Path. **75**:216, 1926.

49. Briggs, W. T., and Maxwell, E. S.: Leucoplakia of the Urinary Tract, J. Urol. **16**:1, 1926.

Bacteriologic data at the present time is not sufficient to justify conclusions other than that infection of some type is usually associated with the lesion; in four cases, however, cultures of the urine were reported negative. The origin is unknown. Irritation in the form of infection or stone, or both, is often present but several cases have been reported in which bacteria were not discovered, and many in which there were no stones. While calculi may cause leukoplakia by irritation, one must not lose sight of the fact that desquamated cornified epithelium may act as a nucleus for stone, especially if infection is present. The symptoms are not pathognomonic. The passage of pieces of membrane, however, should always suggest leukoplakia. Leukoplakia of the bladder does not respond to irrigations or instillations, so resection, electrodesiccation or radium must be relied on, and none of these has been used often enough to judge its value. Since renal leukoplakia is seldom diagnosed before operation or necropsy, nephrectomy will usually be carried out for the associated pathologic lesion and not for leukoplakia.

Nedelec and Vafiadis [50] noted that vesical purpura may become apparent in infancy. Two thirds of the reported cases occurred in the female. The condition usually starts suddenly with fever, abdominal pain, pain in the extremities, dysuria and hematuria. The urine contains red blood cells, epithelial cells and rare hyaline casts. The capacity of the bladder remains normal and cystoscopy reveals round or irregular hemorrhagic areas of various sizes under the mucous membrane; these are situated especially round the trigone, floor of the bladder and the interureteric ridge. There are no signs of cystitis. The diagnosis is simple, especially in the presence of skin changes. Differential diagnosis must be made of tuberculosis, cystitis cystica and hemorrhagic cystitis. The prognosis of purpura is favorable and usually only symptomatic treatment is indicated. A case is described, that of a girl, aged 14, in which two blood transfusions effected cure. Twelve similar cases are cited from the literature.

Exstrophy.—Robinson and Foulds [51] reported the case of a man, aged 23, who was one of the five operated on for exstrophy of the bladder by Peters by his method of transplanting the ureters. This patient came under their care with pyonephrotic sac on the right side, which they drained. The patient recovered and is able to carry on in his trade twenty-one years after the transplantation of the ureters into the rectum.

(To be continued)

50. Nedelec and Vafidis: Étude sur le purpura de la vessie, Arch. d. mal. d. org. gén.-urin. **2**:257, 1925.

51. Robinson, T. A., and Foulds, G. S.: The Late Results After an Operation for Exstrophy of the Bladder, Brit. J. Surg. **14**:529, 1927.